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TUMORIGENIC EVALUATION OF JET FUELS JP-TS AND JP-7

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

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Deputy Director, Toxic Hazards Division
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13. ABSTRACT (Maximum 200 words)

Fischer 344 rats and C57BL/6 mice were exposed for one year to inhalation concentrations of either 200 or 1000 mg JP-TS/m^3 or 150 or 750 mg JP-7/m^3. A common control group of rats and mice exposed to air alone was maintained under similar exposure conditions. Six animals of each species, sex, and group were sacrificed at the termination of the one-year exposure period. All survivors were maintained for an additional one-year observation period. Significant microscopic findings following the one-year inhalation study were primarily restricted to renal lesions found in male rats. The renal lesions were consistent with changes reported following other hydrocarbon inhalation exposures. Renal neoplasms were slightly increased in number in male rats following the postexposure observation period. No exposure-related degenerative changes or increased carcinogenesis was noted in mice.

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PREFACE

This is one of a series of technical reports describing results of the experimental laboratory programs conducted at the Toxic Hazards Research Unit, ManTech Environmental Technology, Inc. This document serves as a final report on the Oncogenic Evaluation of Jet Fuels JP-TS and JP-7. The research described in this report began in March 1981 and was completed in February 1991 under U.S. Air Force Contracts No. F33615-80-C-0512, F33615-85-C-0532, and F33615-90-C-0532. M.K. Pinkerton served as Contract Technical Monitor for the U.S. Air Force, Harry G. Armstrong Aerospace Medical Research Laboratory during the in-life portion of this study.

The authors would like to acknowledge Jeffrey Collins and Jose Diaz for chamber atmosphere analyses and Robin E. Wolfe, Janet L. Wilson, and Susan E. Dille for their assistance in the preparation of this manuscript.

TABLE OF CONTENTS

TABLE OF CONTENTS continued

LIST OF TABLES

LIST OF TABLES continued

LIST OF TABLES continued

LIST OF FIGURES

ABBREVIATIONS

BUN	Blood urea nitrogen
C	Celsius
cfm	Cubic feet per minute
CNS	Central nervous system
dL	Deciliter
F-344	Fischer 344 (rats)
fL	Femtoliter
g	Gram
GC	Gas chromatograph
GC/MS	Gas chromatograph/mass spectrophotometer
h	Hour
HCA	Hydrocarbon analyzer
IU	International Unit
kg	Kilogram
L	Liter
m^3	Cubic meter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mEq	Milliequivalent
mg	Milligram
min	Minute
N	Number
p	Probability
pg	Picogram
psi	Pounds per square inch
RBC	Red blood cells
SEM	Standard error of the mean
SGOT/AST	Serum glutamic-oxalacetic transaminase/Aspartate aminotransferase
SGPT/ALT	Serum glutamic-pyruvic transaminase/Alanine aminotransferase
THRU	Toxic Hazards Research Unit
WBC	White blood cells
wt	Weight
vol	Volume

SECTION 1

INTRODUCTION

The use of jet engines in military and commercial aircraft has led to the development of a number of petroleum distillate fuels with special properties. These fuels are generally less volatile than gasoline fractions used in conventional internal combustion engines. As part of an overall evaluation of Air Force fuels, it was desirable to assess the tumorigenic potential associated with long term inhalation exposure of fuel vapor. The two fuels included in this investigation are JP-TS, a high altitude jet fuel similar in composition to the jet fuel JP-4, and JP-7, which closely resembles the jet fuel designated JP-5. An eight-month inhalation study at 5000 mg JP-4/m^3 produced organ hypertrophy and bronchial irritation in male and female Sprague-Dawley rats and caused central nervous system (CNS) effects and increased osmotic erythrocyte fragility in female beagle dogs (MacEwen and Vernot, 1975). A 90-day continuous exposure study of Fischer 344 (F-344) rats, C57BL/6 mice, and beagle dogs to 1000 and 500 mg JP-4/m^3 resulted in no CNS effects in dogs, nor were any increases in osmotic erythrocyte fragility noted during the course of the study (MacEwen and Vernot, 1980). Both concentrations of JP-4 caused reduced weight gains in male and female rats during the exposure; however, this difference disappeared during the 19-month postexposure observation period.

As a follow-up to the 8-month and 90-day inhalation studies, rats and mice were intermittently exposed to 1000 and 5000 mg JP-4/m^3 for 12 months. The inhalation exposure period was followed by a 12-month holding period for observation of possible oncogenic effects (Bruner et al., 1991). Pathologic findings in male rats revealed treatment-related renal toxicity and neoplasia consistent with male rat $\alpha 2\mu$-globulin nephropathy syndrome. The

study did not produce any target organ toxicity or tumor formation that was considered treatment related.

Continuous exposure (24 h/day, 7 days/week) of F-344 rats, C57BL/6 mice, and beagle dogs to 750 and 150 mg JP-5/m^3 vapors for 90 days resulted in nephropathy characterized by hyaline droplets, casts, and renal tubular necrosis in male rats (Gaworski et al., 1984). Medullary mineralization and accentuated tubular degeneration were noted in male rats held postexposure. No pathologic lesions were observed in dogs exposed to JP-5 vapor.

This study was designed to determine the effects, particularly oncogenic, of long-term exposure of rats and mice to low concentrations of JP-TS and JP-7 fuel vapors. The F-344 rat and C57BL/6 mouse were selected as the test species to afford a comparison with the above-mentioned studies.

SECTION 2

MATERIALS AND METHODS

TEST MATERIALS

JP-TS is a broad mixture of aliphatic and aromatic hydrocarbon compounds defined in terms of physical and chemical characteristics and includes various additives, all of which meet the requirements of Military Specification MIL-T-25524B. Pertinent chemical and physical properties of the fuel detailed in the military specifications are listed below.

Sulfur, max.	0.3% (by wt.)
Mercaptan sulfur, max.	0.001% (by wt.)
Aromatics, max.	20.0% (by vol.)
Distillation:	
Initial boiling point, °F	315
End point, °F	500
Freezing point, °F, max.	-64
Flash point, °F, min.	110
Viscosity, centistokes at -40 °F, max.	12.0

A total ion chromatogram of JP-TS, obtained using gas chromatography/mass spectrometry (GC/MS), is shown in **Figure 1** with identification of some of the major components. These constituents represent only a fraction of the total content of JP-TS jet fuel; the remainder consists of unspecified hydrocarbon compounds in the kerosene boiling range.

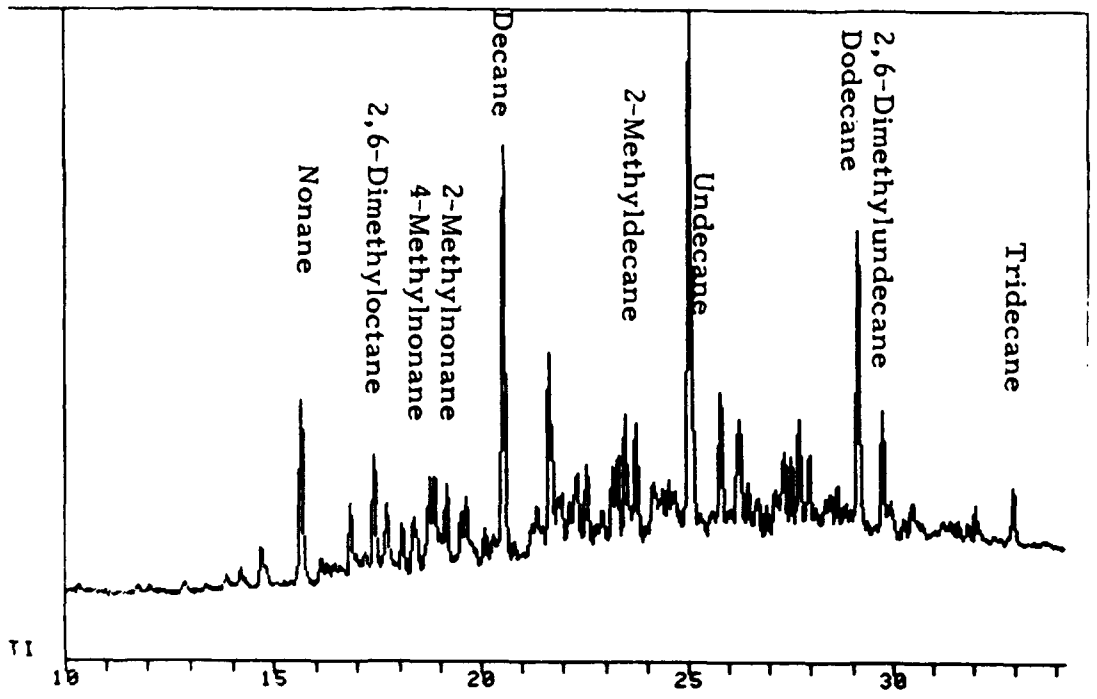


Figure 1. Total Ion Chromatogram of JP-TS by GC/MS.

JP-7 is a complex mixture of hydrocarbon compounds that is defined in terms of physical and chemical characteristics and includes various additives, all of which meet the requirements of Military Specification MIL-T-38219A. The specified physical and chemical parameters are detailed below.

Sulfur, max.	0.1% (by wt.)
Mercaptan sulfur, max:	0.001% (by wt.)
Aromatics, max.	5% (by vol.)
Distillation:	
Initial boiling point, °F	360
End point, °F	550
Freezing point, °F, max.	-43.5
Flash point, °F, min.	140
Viscosity, centistokes at -20 °C, max.	8.0
Density, kg/m^3, min. at 15 °C	779
Density, kg/m3, max. at 15 °C	806
Vapor pressure, kPa (psi) at 149 °C, max.	3.0

A total ion chromatogram of JP-7, obtained by GC/MS, is shown in **Figure 2** and illustrates the narrow range of components in this fuel. Five components have been identified but further identification of the mixture is difficult because of overlapping and poor separation of peaks.

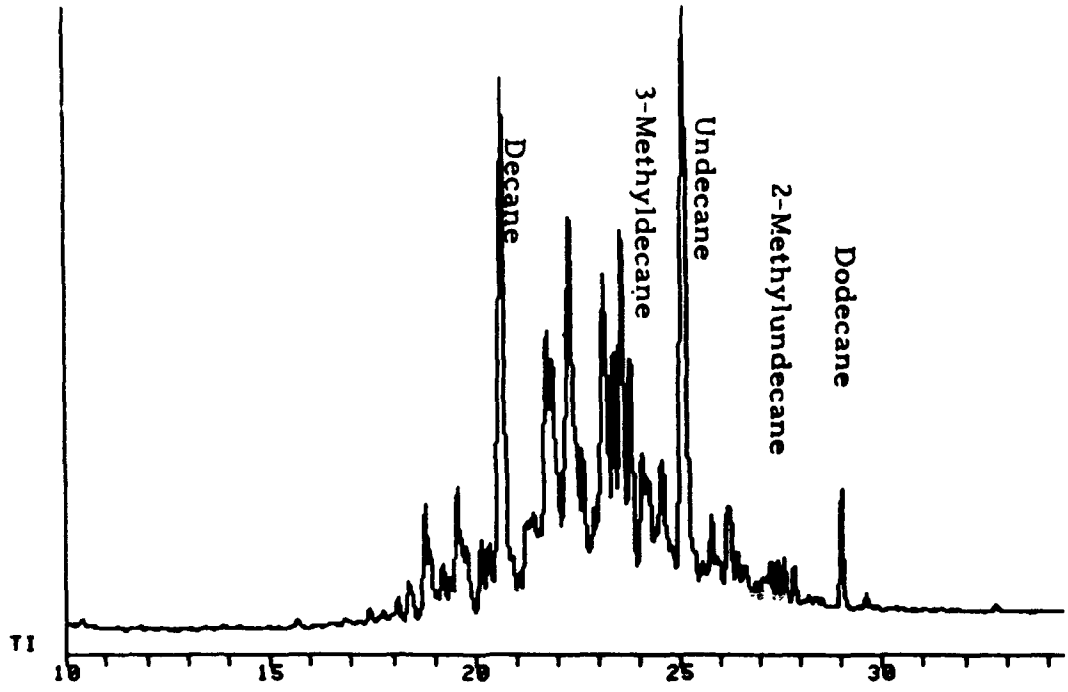


Figure 2. Total Ion Chromatogram of JP-7 by GC/MS.

TEST AGENT QUALITY CONTROL

Twenty-five barrels of JP-TS were received from the U.S. Air Force for use in these studies. Before initiating animal exposures, the JP-TS was subjected to quality control procedures. Samples of fuel were taken from all 25 barrels and injected into a gas chromatograph (GC) for fingerprint analyses. The percent of total area under the chromatogram was calculated for each of the five major peaks (**Appendix A**) to ensure that all barrels were supplied from the same production batch. All barrels were found to be acceptable and the first 15 were used in the animal exposures. The remaining barrels were returned to the Air Force.

Twenty-five 55-gallon drums of JP-7 were obtained and individually identified for this study. Quality control consisted of obtaining GC fingerprints from each barrel of JP-7. **Appendix B** shows the results of the initial quality control work. These samples were all analyzed before the start of the study and the same ten largest peaks from each chromatogram were selected for comparison. The area under the peaks was measured with a computing integrator. Drum #017 was seen as the only sample with a significant number of peaks outside the range of the other samples and was not used in this study.

Quality control evaluations of both fuels were accomplished using a Varian 3700 GC (Varian Associates, Palo Alto, CA) with a 50 m, 0.25 mm ID, SP21000 capillary column (Supelco Corp., Bellefonte, PA). A Hewlett-Packard 3388 computing integrator

(Hewlett-Packard Corp., Palo Alto, CA) was used to measure peak areas and record data. Chromatograph conditions were as follows:

Sample:	0.1 µL; split 10/1 (JP-TS)
	0.1 µL; split 200/1 (JP-7)
FID temp:	250 °C
Injector temp:	250 °C
Column initial temp:	33 °C for 6 minutes
Final temp:	230 °C for 2 minutes

ANIMALS

F-344 rats were purchased from Charles River Breeding Labs, Kingston, NY; C57BL/6 mice were purchased from Jackson Laboratories, Bar Harbor, ME. The rats were 9 weeks of age and the mice 10 weeks of age at exposure initiation. Quality control assessments, conducted during a two-week quarantine period, showed the animals to be in acceptable health.

The animals were group housed in stainless steel cages in conformance with ILAR standards (National Institute of Health Publication #85-23, 1985) for laboratory animal care. All animals were provided food (Purina Formulab 5008) during nonexposure hours and softened water ad libitum. Ambient temperatures were maintained at 21 to 25 °C.

CONTAMINANT GENERATION SYSTEM

The vapor generation systems for JP-TS and JP-7 were identical. A schematic of the generation systems is provided in **Figure 3**. The fuel was pumped under low pressure (8.0 psi) from 55-gallon supply containers to two heated evaporation towers. As the fuel flowed down the tower, a countercurrent airflow (5 cfm) stripped the volatile portions of the fuels. The output of each tower was split to provide the proper vapor concentration to each exposure chamber.

The evaporation towers were maintained at a constant temperature of 50 °C. The unvolatilized fuel was removed via the bottom of the tower where it flowed into a holding tank prior to being pumped into a waste drum. Temperature sensors monitored evaporator temperature at both the top and the bottom of the towers. If the temperatures exceeded 60 °C, an alarm was activated and fuel flow and tower heat were automatically shut off. Fuel flow and tower heat were also automatically stopped in the event of chamber air flow loss. The fuel supply and waste drums were maintained within safety cabinets. These cabinets were ventilated and grounded.

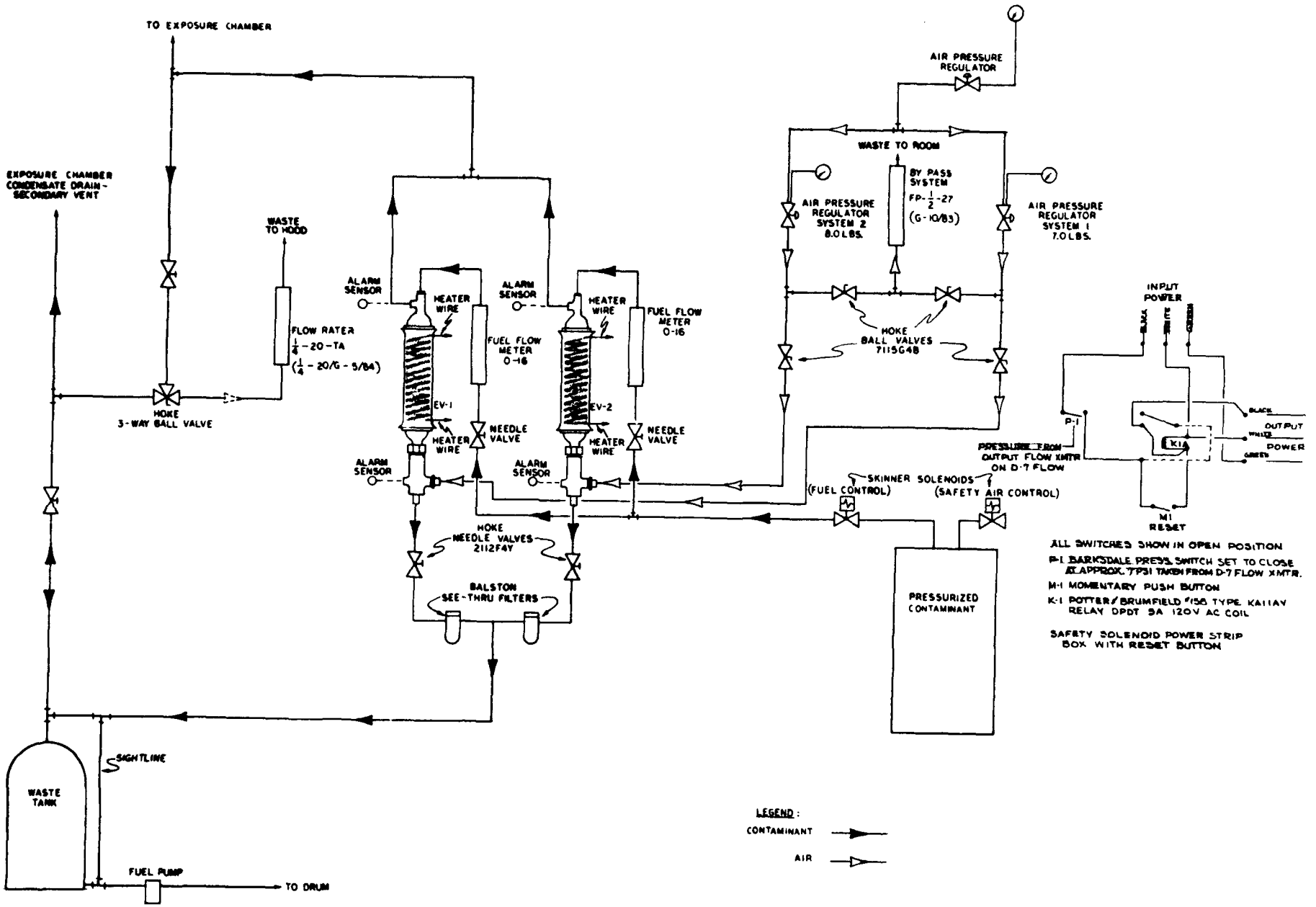


Figure 3. Fuel Introduction System.

CONTAMINANT ANALYTICAL SYSTEM

Exposure chamber concentrations were continuously monitored using a Beckman Model 400 (Fullerton, CA) total hydrocarbon analyzer (HCA). Sample flow through the HCA was maintained at 3 L/min at 5 psi with output measurements plotted on a strip chart recorder. The recorder was equipped with an alarm which would signal if the chamber concentration reached preset high or low values. **Figure 4** provides a schematic view of the analytical system. There was a separate system for each exposure chamber with a common hydrogen and air supply. Calibration of the HCA was accomplished using n-heptane as a standard. The response of the HCA to heptane was determined to be the same as the two fuels. Calibration standards were prepared by injecting known amounts of liquid heptane into Mylar^{R} bags containing metered amounts of air. Chamber concentrations were calculated by recording average concentrations every half hour during the daily 6-h exposure period and then computing daily and monthly mean concentrations.

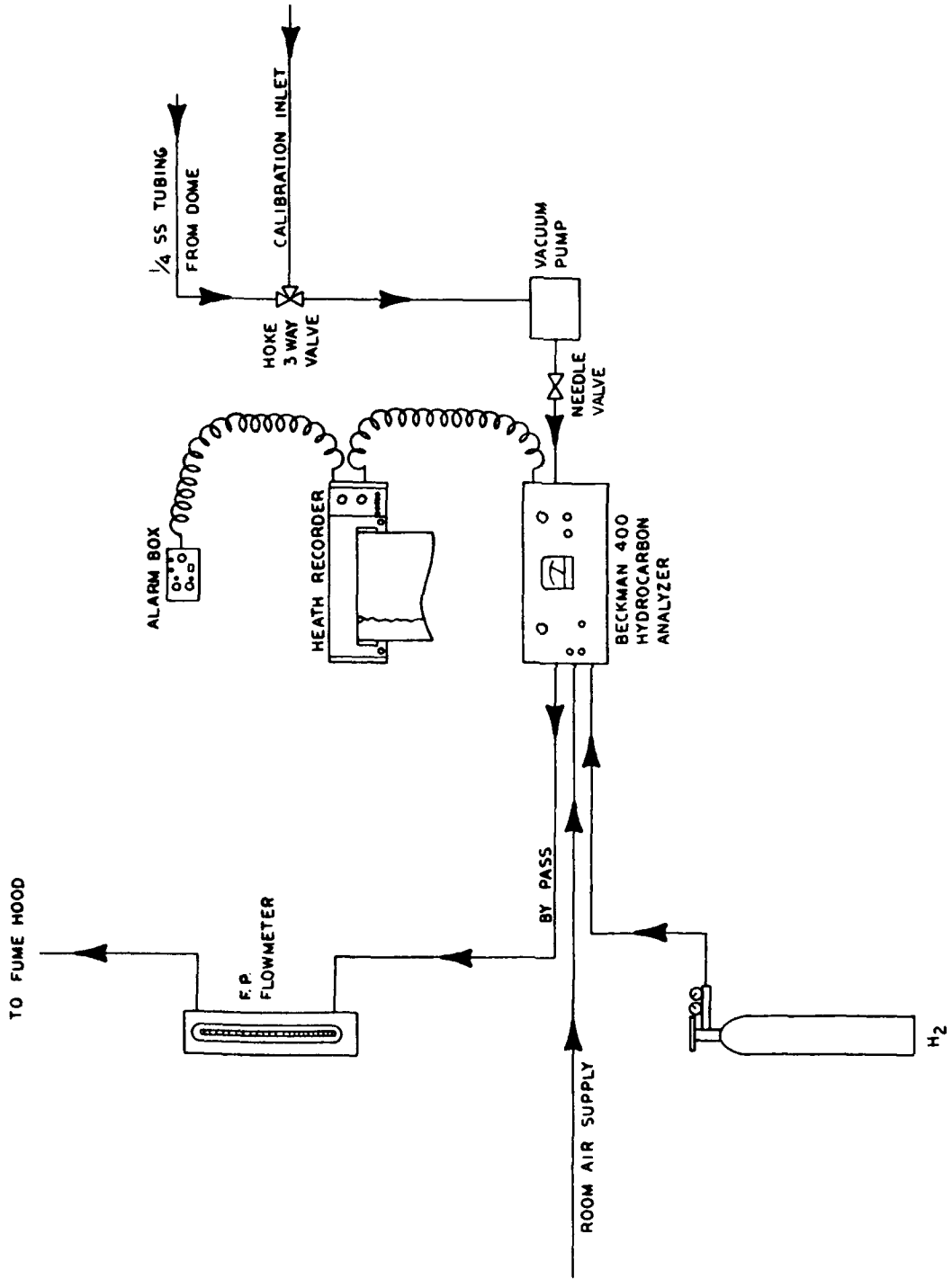


Figure 4. A Schematic Diagram of the JP-TS/JP-7 Analytical System.

EXPOSURE REGIMEN

Male and female mice and rats were exposed to fuel vapor in Thomas Dome chambers for one year using an industrial work week schedule of 6 h/day, 5 days/week with holidays and weekends excluded to simulate a human exposure regimen. Five chambers were utilized to provide exposure concentrations of either air only, 200 mg JP-TS/m^3, 1000 mg JP-TS/m^3, 150 mg JP-7/m^3, or 750 mg JP-7/m^3. Each chamber housed 100 male and 100 female F-344 rats and 100 male and 100 female C57BL/6 mice.

ANIMAL RESPONSE ASSESSMENTS

Rats were individually weighed at biweekly intervals during exposure and monthly thereafter. Mice were weighed in groups with the group mean weight followed on a monthly basis throughout the exposure period. Following the one-year exposure period, six rats and six mice of each sex/group were sacrificed and tissues prepared for histopathologic examination. The remaining animals were sacrificed following a one-year postexposure observation period. Euthanasia was via halothane inhalation overdose. All animals that died or were sacrificed during the study were necropsied and tissues were collected for histopathologic examination. Wet tissue weights were determined on liver, kidney, and spleen from all rats sacrificed at the conclusion of the one-year exposure period. Tissues for histopathologic examination were fixed in a 10% neutral buffered formalin, trimmed, and further processed via routine methods for hematoxylin-eosin stained paraffin-embedded sections (Luna, 1968). Additional kidney sections from all male rats were stained with Mallory Heidenhain's stain to evaluate hyaline droplets in proximal tubular epithelium.

Additionally, blood was drawn via the portal vein from all rats sacrificed at the exposure phase termination for evaluations listed in **Table 1**. Samples were obtained from fasted animals.

Clinical chemistry analyses were performed with a DuPont automated clinical analyzer (E.I. DuPont de Nemours & Co., Inc., Wilmington, DE). A Coulter S-Plus blood analyzer (Coulter Instruments, Hialeah, FL) was used to obtain most hematologic values. Absolute leukocyte differentials were determined according to established procedures.

Table 1. Clinical Hematology and Chemistry Tests Performed on Rats Exposed to Fuel Vapor

Hematology	Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Red Blood Cells (RBC)	Calcium
White Blood Cells (WBC)	Albumin/Globulin
Differentials	Total Protein
Mean Corpuscular Volume (MCV)	Glucose
Mean Corpuscular Hemoglobin (MCH)	Alkaline Phosphatase
Mean Corpuscular Hemoglobin Concentration (MCHC)	SGPT/ALT
	SGOT/AST
	Bilirubin
	Creatinine
	BUN

STATISTICS

Data from routine animal weighing, hematology, blood chemistry, and organ weighings were analyzed for statistical significance using an analysis of variance with Scheffe multiple comparisons (Barcikowski, 1983; Dixon, 1985). Pathologic lesion incidence was analyzed using the Chi-square test for equality of proportion (Fleiss, 1981).

SECTION 3

RESULTS

The specified target concentrations were maintained during the one-year exposure period. Chamber monthly mean concentrations were maintained within ±5% of the target concentrations. The overall mean concentrations for the targeted 200 and 1000 mg JP-TS/m^3 exposures were 200.4 ± 3.0 and 1000.2 ± 16.1 mg JP-TS/m^3, respectively (**Table 2**). The overall mean concentrations for the targeted 150 and 750 mg JP-7/m^3 exposures were 150.1 ± 4.7 and 750.4 ± 19.1 mg JP-7/m^3, respectively.

Clinical signs of toxic stress were not apparent during or following the one-year inhalation exposure regimen. No differences were noted in rate of death in male or female rats exposed to either JP-TS or JP-7 vapor (**Figures 5** and **6**). Male mice exposed at 150 mg JP-7/m^3 died at a rate greater than controls ($p<0.01$), primarily during the one-year postexposure observation period (**Figures 7** and **8**). Mortality in the other mouse groups was not different than their respective control groups.

Mean body weights for male and female rat groups are provided in **Figures 9** and **10** and in **Appendices C** through **F**. Both groups of fuel-exposed male rats showed a slight depression in mean body weight throughout the two-year study period.

Table 2. Summary of Exposure Concentration[a] Information

	JP-7		JP-TS	
	Low	High	Low	High
Target Concentration, mg/m^3	150	750	200	1000
Mean ± S.D., mg/m^3	150.1 ± 4.7	750.3 ± 19.1	200.4 ± 3.1	1000.2 ± 16.1
High[b], mg/m^3	154.8	772.2	202.1	1010.0
Low[b], mg/m^3	147.4	737.8	198.6	993.4

[a]The overall mean concentration is a mean of monthly mean concentrations.

[b]Monthly mean concentration.

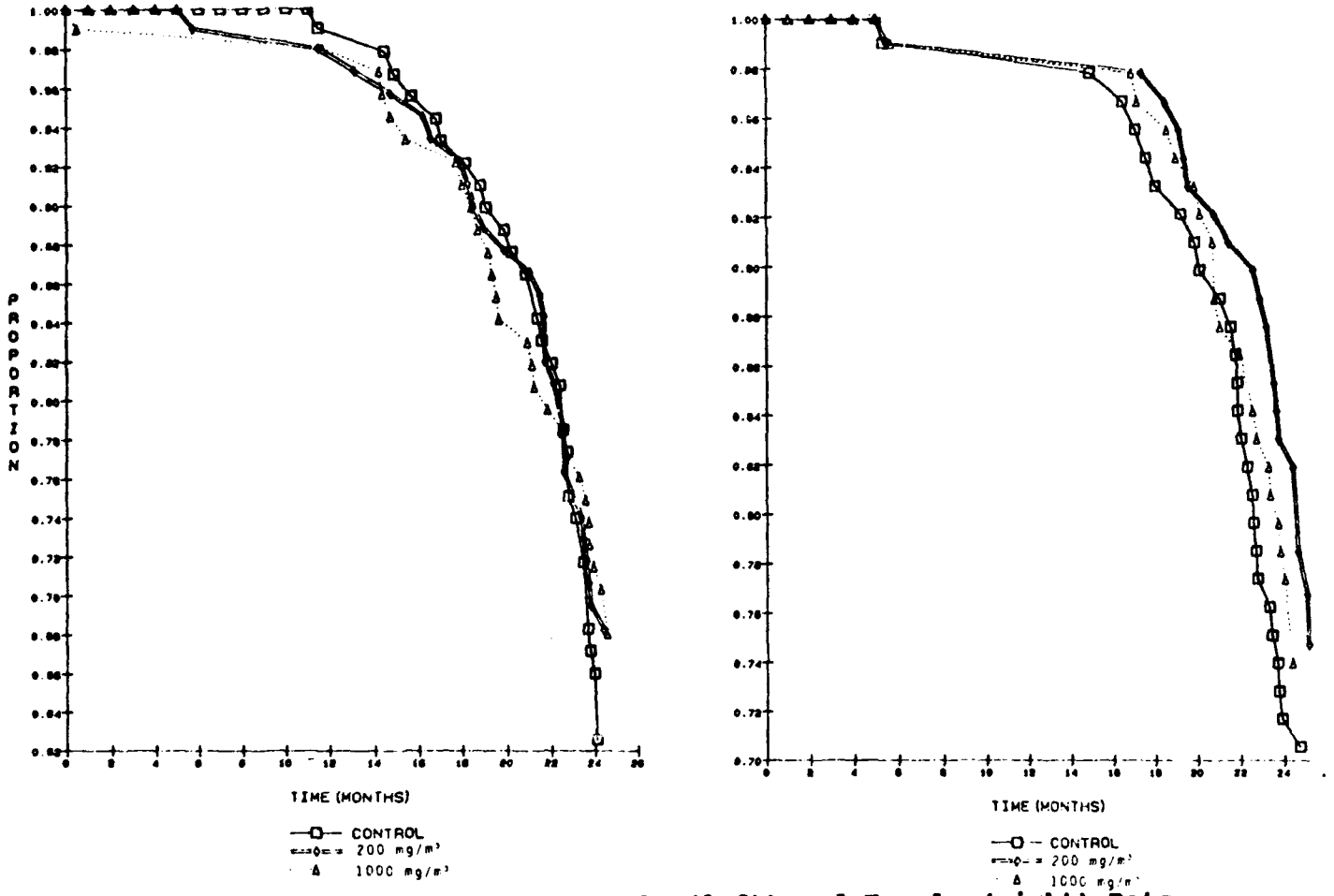


Figure 5. Survival Data for Male (left) and Female (right) Rats. Animals were exposed to JP-TS vapor for one year and then maintained for a one-year postexposure period.

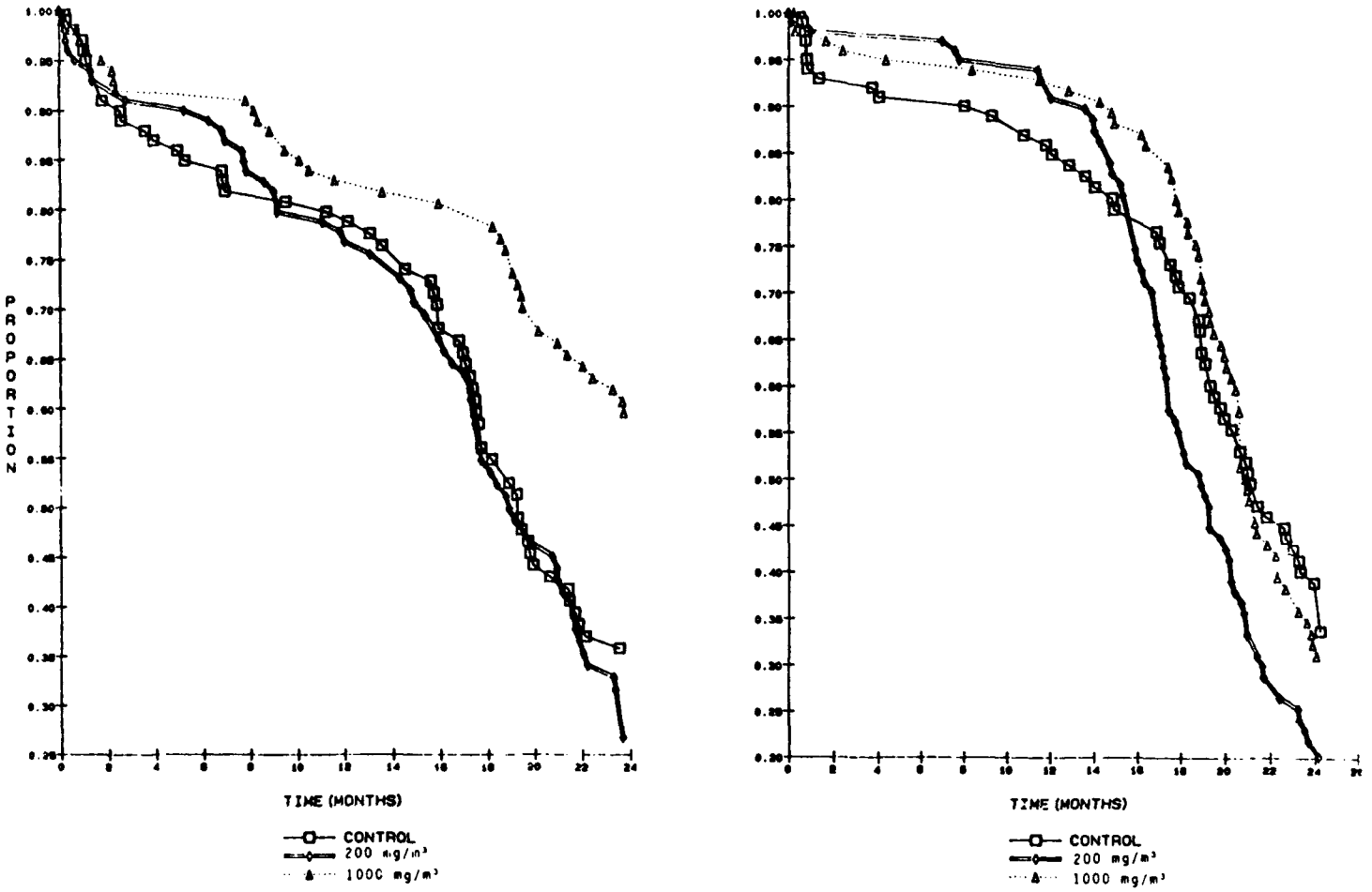


Figure 6. Survival Data for Male (left) and Female (right) Mice. Animals were exposed to JP-TS vapor for one year and then maintained for a one-year postexposure period.

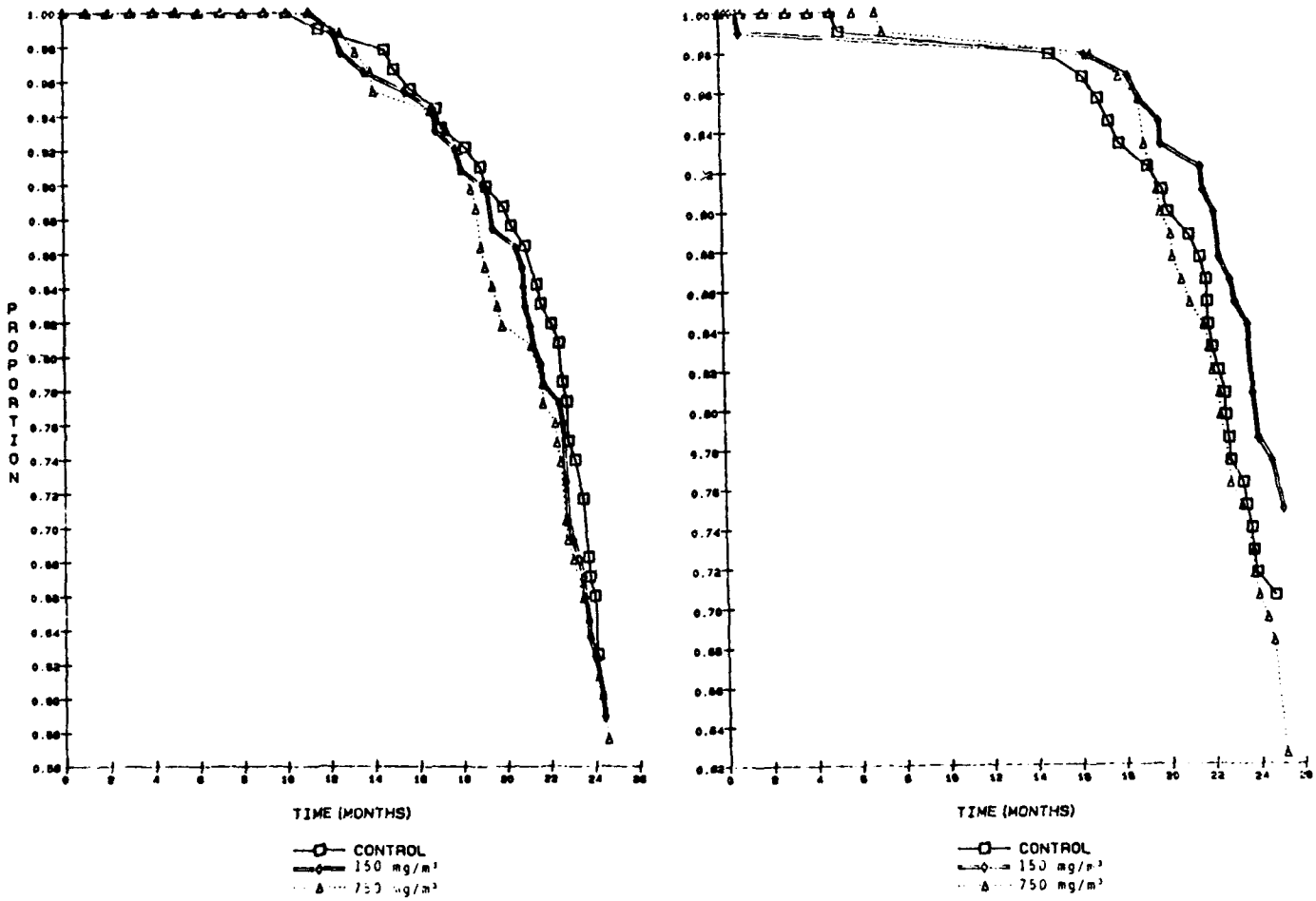


Figure 7. Survival Data for Male (left) and Female (right) Rats. Animals were exposed to JP-7 vapor for one year and then maintained for a one-year postexposure period.

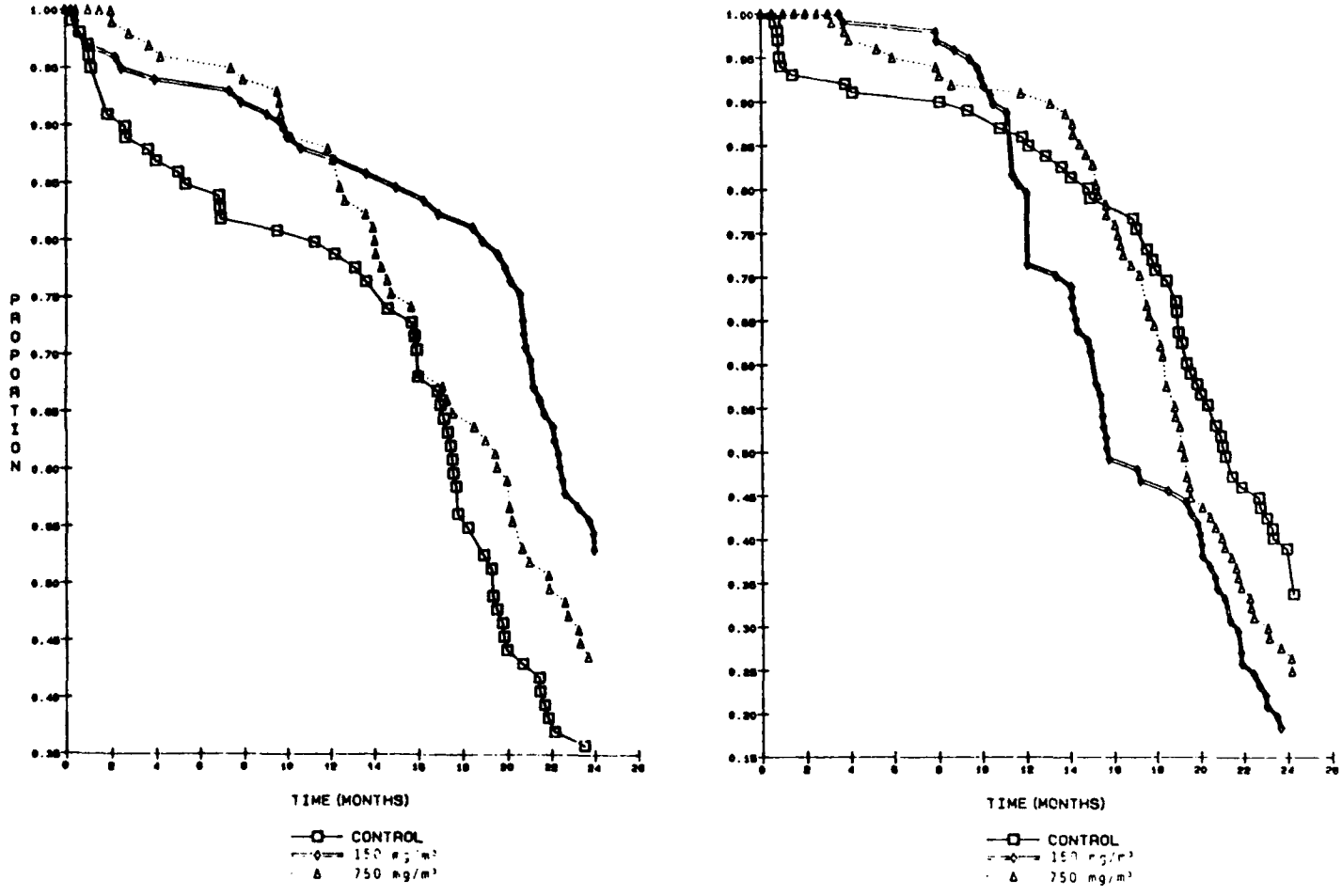


Figure 8. Survival Data for Male (left) and Female (right) Mice. Animals were exposed to JP-7 vapor for one year and then maintained for a one-year postexposure period.

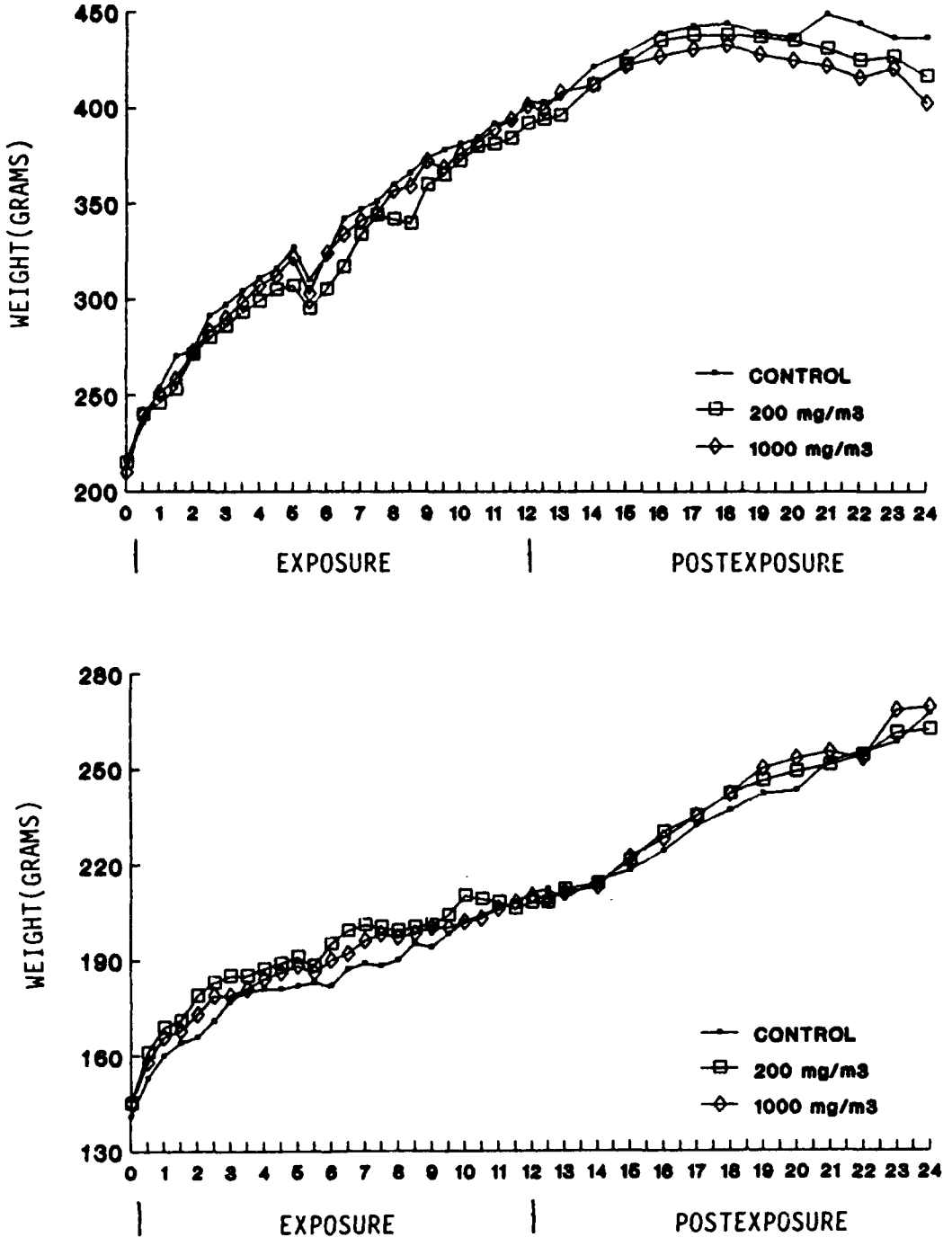


Figure 9. Body Weight Means for Male (top) and Female (bottom) F-344 Rats Exposed to JP-T8 Vapor for One Year.

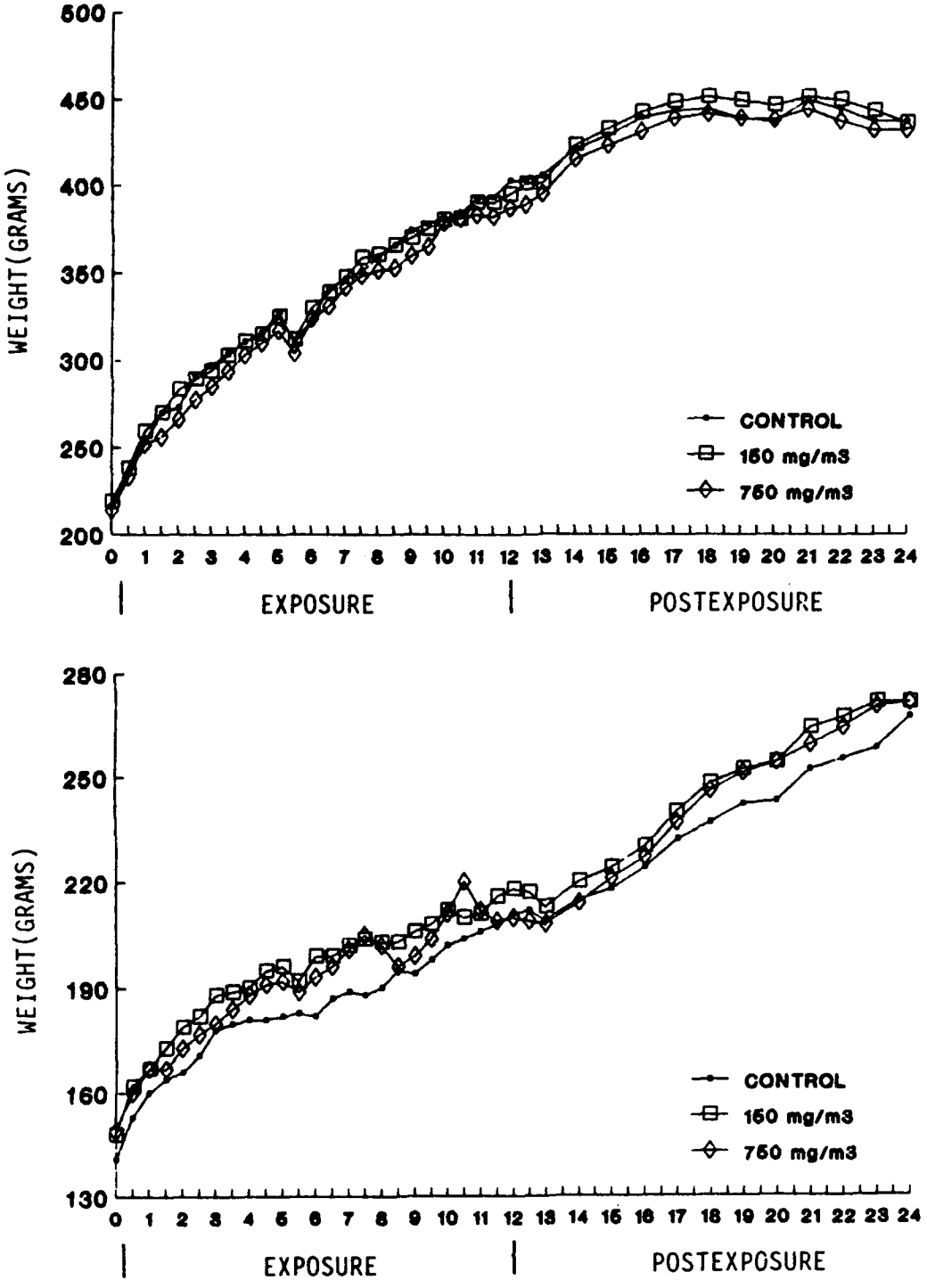


Figure 10. Body Weight Means for Male (top) and Female (bottom) F-344 Rats Exposed to JP-7 Vapor for One Year.

Hematology and blood chemistry data from these animals are listed in **Tables 3** through **6**. Creatinine and blood urea nitrogen (BUN) values were increased ($p<0.01$) in male rats exposed at both concentrations of JP-TS. A decrease ($p<0.01$) in glucose values was noted in both groups of female rats exposed to JP-TS vapor. Significant increases ($p<0.01$) in potassium and sodium were found in female rats exposed to the higher concentration of JP-TS vapor while mean corpuscular hemoglobin (MCH) was significantly different from controls ($p<0.01$) only in the low concentration group.

Male rats exposed at the high concentration of JP-7 had increased ($p<0.01$) total protein, globulin, creatinine, and BUN values. Male rats exposed at the low concentration had a significant increase ($p<0.01$) in alkaline phosphatase as well as BUN values. White blood cell count was also found to be significantly ($p<0.01$) different from control values in the low concentration male rats. No treatment-related effects in blood chemistries were noted in the JP-7 exposed female rats. The only parameter that was different from control values was the alkaline phosphatase level of the low concentration female rat group.

Table 3. Blood Values[a] of Male Rats at Termination of One-Year Exposure to JP-TS

	Control	200 mg/m^3	1000 mg/m^3
RBC (10^6)	8.5 ± 0.2	8.3 ± 0.2	8.8 ± 0.1
WBC (10^3)	5.1 ± 0.2	4.7 ± 0.2	4.5 ± 0.2
HCT (%)	49.0 ± 0.4	47.6 ± 0.3	48.4 ± 0.4
HGB (g/dL)	16.0 ± 0.1	16.0 ± 0.2	16.0 ± 0.1
Total Protein (g/dL)	7.6 ± 0.1	7.8 ± 0.1	7.8 ± 0.1
Albumin (g/dL)	4.0 ± 0.1	4.0 ±<0.1	4.0 ± 0.1
Globulin (g/dL)	3.6 ± 0.1	3.8 ± 0.1	3.8 ±<0.1
A/G Ratio (%)	1.1 ±<0.1	1.1 ±<0.1	1.1 ±<0.1
Glucose (mg/dL)	198.2 ± 7.4	177.5 ± 8.9	184.0 ± 6.4
Calcium (mg/dL)	11.2 ± 0.1	11.2 ± 0.1	11.3 ± 0.1
Potassium (mEq/L)	6.5 ± 0.3	6.2 ± 0.3	5.9 ± 0.1
Sodium (mEq/L)	154.7 ± 0.4	156.8 ± 0.8	156.2 ± 1.1
Bilirubin (mg/dL)	043 ±<0.1	0.5 ±<0.1	0.5 ±<0.1
Creatinine (mg/dL)	0.5 ±<0.1	0.6 ±<0.1[b]	0.6 ±<0.1[b]
SGPT/ALT (IU/L)	54.4 ± 6.2	50.6 ± 4.9	50.0 ± 9.3
SGOT/AST (IU/L)	95.7 ± 5.7	91.9 ± 3.7	151.8 ± 67.2
Alk. Phos. (IU/L)	8.6 ± 0.6	9.9 ± 0.7	9.1 ± 0.4
BUN (mg/dL)	11.4 ± 0.4	13.0 ± 0.4[b]	13.3 ± 0.2[b]
MCV (fL)	58.3 ± 1.3	57.7 ± 1.0	54.7 ± 0.5
MCH (pg)	19.0 ± 0.5	19.3 ± 0.3	18.1 ± 0.3
MCHC (g/dL)	32.6 ± 0.3	33.5 ± 0.3	33.1 ± 0.3

[a]Mean ± SEM, N=10.
[b]Significantly different from control, $p<0.01$, as determined by a two-factorial analysis of variance.

Table 4. Blood Values[a] of Female Rats at Termination of One-Year Exposure to JP-TS

	Control	200 mg/m^3	1000 mg/m^3
RBC (10^6)	7.9 ± 0.2	7.0 ± 0.3	7.4 ± 0.4
WBC (10^3)	3.4 ± 0.1	3.0 ± 0.2	3.1 ± 0.1
HCT (%)	46.6 ± 0.5	45.6 ± 0.8	46.1 ± 0.6
HGB (g/dL)	15.6 ± 0.3	15.1 ± 0.5	15.8 ± 0.3
Total Protein (g/dL)	7.7 ± 0.1	7.6 ± 0.1	7.7 ± 0.1
Albumin (g/dL)	3.8 ± 0.1	3.7 ± 0.1	3.8 ± 0.1
Globulin (g/dL)	3.9 ± 0.1	3.9 ± 0.1	3.9 ±<0.1
A/G Ratio (%)	1.0 ±<0.1	0.9 ±<0.1	1.0 ±<0.1
Glucose (mg/dL)	139.6 ± 6.8	106.7 ± 8.2[b]	114.6 ± 5.0[b]
Calcium (mg/dL)	11.3 ± 0.2	11.5 ± 0.1	11.4 ± 0.1
Potassium (mEq/L)	5.0 ± 0.2	5.3 ± 0.1	6.0 ± 0.2[b]
Sodium (mEq/L)	153.2 ± 0.7	154.7 ± 1.3	157.3 ± 1.0[b]
Bilirubin (mg/dL)	0.3 ±<0.1	0.2 ±<0.1	0.2 ±<0.1
Creatinine (mg/dL)	0.5 ±<0.1	0.5 ±<0.1	0.4 ±<0.1
SGPT/ALT (IU/L)	53.4 ± 6.6	51.6 ± 4.1	41.4 ± 2.1
SGOT/AST (IU/L)	102.7 ±13.4	96.1 ± 4.5	89.8 ± 3.5
Alk. Phos. (IU/L)	6.0 ± 0.5	6.3 ± 0.6	6.4 ± 0.5
BUN (mg/dL)	13.8 ± 0.6	13.9 ± 0.7	13.7 ± 0.4
MCV (fL)	58.9 ± 1.2	65.9 ± 2.3	65.3 ± 6.5
MCH (pg)	19.7 ± 0.3	21.7 ± 0.5[b]	22.4 ± 2.4
MCHC (g/dL)	33.4 ± 0.3	33.1 ± 0.6	34.2 ± 0.5

[a]Mean ± SEM, N=10.

[b]Significantly different from control, $p<0.01$, as determined by a two-factorial analysis of variance.

Table 5. Blood Values[a] of Male Rats at Termination of One-Year Exposure to JP-7

	Control	150 mg/m^3	750 mg/m^3
RBC (10^6)	8.5 ± 0.2	7.9 ± 0.2	8.4 ± 0.2
WBC (10^3)	5.1 ± 0.2	4.3 ± 0.2[b]	4.4 ± 0.1
HCT (%)	49.0 ± 0.4	46.9 ± 0.3	48.6 ± 0.4
HGB (g/dL)	16.0 ± 0.1	15.8 ± 0.2	16.2 ± 0.2
Total Protein (g/dL)	7.6 ± 0.1	7.7 ± 0.1	8.0 ± 0.1[b]
Albumin (g/dL)	4.0 ± 0.1	4.0 ±<0.1	4.1 ± 0.1
Globulin (g/dL)	3.6 ± 0.1	3.6 ± 0.1	3.8 ±<0.1[b]
A/G Ratio (%)	1.1 ±<0.1	1.1 ±<0.1	1.1 ±<0.1
Glucose (mg/dL)	198.2 ± 7.4	193.3 ± 7.1	195.9 ± 4.5
Calcium (mg/dL)	11.2 ± 0.1	11.3 ± 0.1	11.4 ± 0.1
Potassium (mEq/L)	6.5 ± 0.3	6.3 ± 0.3	6.1 ± 0.3
Sodium (mEq/L)	154.7 ± 0.4	157.3 ± 0.4	155.9 ± 0.7
Bilirubin (mg/dL)	0.4 ±<0.1	0.5 ± 0.1	0.4 ±<0.1
Creatinine (mg/dL)	0.5 ±<0.1	0.5 ±<0.1	0.6 ±<0.1[b]
SGPT/ALT (IU/L)	54.4 ± 6.2	53.2 ± 4.0	41.6 ± 3.8
SGOT/AST (IU/L)	95.7 ± 5.7	104.7 ± 6.0	85.8 ± 3.0
Alk. Phos. (IU/L)	8.6 ± 0.6	10.9 ± 0.5[b]	10.3 ± 0.4
BUN (mg/dL)	11.4 ± 0.4	13.1 ± 0.6[b]	13.0 ± 0.2[b]
MCV (fL)	58.3 ± 1.3	59.7 ± 1.5	57.8 ± 0.8
MCH (pg)	19.0 ± 0.5	20.0 ± 0.3	19.2 ± 0.2
MCHC (g/dL)	32.6 ± 0.3	33.7 ± 0.5	33.3 ± 0.3

[a]Mean ± SEM, N=10.

[b]Significantly different from control, $p<0.01$, as determined by a two-factorial analysis of variance.

Table 6. Blood Values[a] of Female Rats at Termination of One-Year Exposure to JP-7

	Control	150 mg/m^3	750 mg/m^3
RBC (10^6)	7.9 ± 0.2	7.2 ± 0.2	7.8 ± 0.1
WBC (10^3)	3.4 ± 0.1	3.2 ± 0.2	3.3 ± 0.1
HCT (%)	46.6 ± 0.5	45.2 ± 0.5	45.8 ± 0.6
HGB (g/dL)	15.6 ± 0.3	15.5 ± 0.2	15.6 ± 0.2
Total Protein (g/dL)	7.7 ± 0.1	7.6 ± 0.2	7.7 ± 0.1[d]
Albumin (g/dL)	3.8 ± 0.1	4.0 ± 0.1	3.8 ± 0.1
Globulin (g/dL)	3.9 ± 0.1	3.6 ± 0.1[b]	4.0 ± 0.1[d]
A/G Ratio (%)	0.9 ±<0.1	1.1 ±<0.1[b]	0.9 ±<0.1[d]
Glucose (mg/dL)	139.6 ± 6.8	143.9 ± 3.2	146.7 ± 7.2[c]
Calcium (mg/dL)	11.3 ± 0.2	11.9 ± 0.2	11.5 ± 0.1[d]
Potassium (mEq/L)	5.0 ± 0.2	5.7 ± 0.2[c]	5.5 ± 0.2[e]
Sodium (mEq/L)	153.2 ± 0.7	156.3 ± 0.8[c]	156.1 ± 0.7[e]
Bilirubin (mg/dL)	0.3 ±<0.1	0.4 ±<0.1	0.2 ±<0.1[c]
Creatinine (mg/dL)	0.5 ±<0.1	0.5 ±<0.1	0.5 ±<0.1[c]
SGPT/ALT (IU/L)	53.4 ± 6.6	51.8 ± 3.3	46.7 ± 4.3[c]
SGOT/AST (IU/L)	102.7 ±13.4	108.1 ± 8.8	97.2 ± 7.3[c]
Alk. Phos. (IU/L)	6.0 ± 0.5	8.5 ± 0.8[b]	8.1 ± 0.6
BUN (mg/dL)	13.8 ± 0.6	13.1 ± 0.6	14.3 ± 0.5[c]
MCV (fL)	58.9 ± 1.2	62.8 ± 1.8	58.9 ± 1.2
MCH (pg)	19.7 ± 0.3	21.5 ± 0.6	20.1 ± 0.4
MCHC (g/dL)	33.4 ± 0.3	34.2 ± 0.5	34.1 ± 0.3

[a] Mean ± SEM, N=10.
[b] Significantly different from control, $p<0.01$, as determined by a two-factorial analysis of variance.
[c] N=9.
[d] N=8.
[e] N=7.

No significant concentration-related differences in mean absolute or relative organ weights were observed in either sex of rats exposed to JP-TS vapor for one year (**Table 7**). A significant decrease ($p<0.05$) in absolute spleen weight in the high concentration JP-7 female rats was noted at necropsy (**Table 8**). Additionally, absolute liver weights were increased ($p<0.05$) in the low concentration JP-7 female rats. Neither of these organs were significantly different from control values when corrected for differences in whole body weight.

Table 7. Mean[a] Organ Weights (g) and Organ-to-Body Weight Ratios (%) of Rats Exposed to JP-TS Vapor for One Year

	Control	200 mg/m^3	1000 mg/m^3
		Male Rats	
Liver	10.21 ± 0.26	10.05 ± 0.31	9.47 ± 0.30
Ratio[b]	2.55 ± 0.06	2.49 ± 0.05	2.43 ± 0.06
Kidney	2.53 ± 0.05	2.51 ± 0.06	2.40 ± 0.06
Ratio	0.63 ± 0.01	0.62 ± 0.01	0.61 ± 0.01
Spleen	0.68 ± 0.05	0.66 ± 0.02	0.62 ± 0.02
Ratio	0.17 ± 0.01	0.16 ±<0.01	0.16 ±<0.01
Whole Body	400.5 ± 5.1	404.1 ± 7.7	390.4 ± 6.8
		Female Rats	
Liver	4.56 ± 0.08	4.45 ± 0.14	4.37 ± 0.14
Ratio	2.23 ± 0.04	2.23 ± 0.05	2.17 ± 0.08
Kidney	1.38 ± 0.03	1.36 ± 0.04	1.40 ± 0.03
Ratio	0.67 ± 0.01	0.69 ± 0.01	0.69 ± 0.02
Spleen	0.42 ± 0.02	0.41 ± 0.01	0.40 ± 0.01
Ratio	0.20 ± 0.01	0.21 ±<0.01	0.20 ± 0.01
Whole Body	205.0 ± 2.8	199.2 ± 5.1	201.8 ± 3.6

[a]Mean ± SEM, N=10 rats/group.
[b]Organ weight/Body weight x 100.

Table 8. Mean[a] Organ Weights (g) and Organ-to-Body Weight Ratios (%) of Rats Exposed to JP-7 Vapor for One Year

	Control	150 mg/m^3	750 mg/m^3
		Male Rats	
Liver	10.21 ± 0.26	10.19 ± 0.20	10.08 ± 0.18
Ratio[b]	2.55 ± 0.06	2.57 ± 0.03	2.57 ± 0.04
Kidney	2.53 ± 0.05	2.51 ± 0.07	2.41 ± 0.02
Ratio	0.63 ± 0.01	0.63 ± 0.01	0.62 ± 0.01
Spleen	0.68 ± 0.04	0.64 ± 0.02	0.61 ± 0.01
Ratio	0.17 ± 0.01	0.16 ± 0.01	0.16 ±<0.01
Whole Body	400.5 ± 5.1	396.0 ± 5.8	392.0 ± 4.7
		Female Rats	
Liver	4.56 ± 0.08	5.01 ± 0.14[c]	4.84 ± 0.17
Ratio	2.23 ± 0.04	2.31 ± 0.06	2.36 ± 0.07
Kidney	1.38 ± 0.03	1.38 ± 0.02	1.34 ± 0.03
Ratio	0.67 ± 0.01	0.64 ± 0.01	0.65 ± 0.01
Spleen	0.42 ± 0.02	0.39 ± 0.01	0.38 ± 0.01[c]
Ratio	0.20 ± 0.01	0.18 ±<0.01	0.18 ±<0.01
Whole Body	205.0 ± 2.8	216.9 ± 3.9[c]	205.3 ± 3.9

[a]Mean ± SEM, N=10.
[b]Organ weight/Body weight x 100.
[c]Different from controls at 0.05 level of significance.

Treatment-related nonneoplastic lesions noted histopathologically in rats following the one-year exposure period included renal mineralization of moderate severity in male rats exposed at 1000 mg JP-TS/m^3 (**Table 9**). This lesion persisted and was exposure-related for incidence and severity following the postexposure holding period (**Table 10**). While this lesion was not noted in JP-7-exposed male rats at the conclusion of the exposure period (**Table 11**), results following the one-year postexposure period were not unlike those found in their counterparts exposed to JP-TS vapor (**Table 12**). Pelvic hyperplasia, occurring only in the male rats held postexposure, was treatment-related, but of greater incidence in the JP-TS-exposed animals. Progressive rat nephropathy was noted primarily in males, both test and control, immediately following the exposure period. Incidence and severity were increased in both sexes (but to a greater extent in males), at the conclusion of the one-year observation period.

Hydronephrosis occurred primarily in male rats with a single case noted in a female rat. Except for the low concentration JP-TS rats held postexposure, the incidence of this lesion was higher in all test groups than was found in controls. The incidence of hyaline droplets was found to range from 99 to 100% in all male rat groups.

Thyroid C-cell hyperplasia was present in more than 50% of male and female rat control groups at both sacrifice periods (**Tables 13** through **16**). In both the JP-TS and the JP-7 groups sacrificed immediately following exposure and those sacrificed following a one-year holding period, the incidence of C-cell hyperplasia was usually greater in the control group, actually showing a treatment-related decrease in incidence in exposure groups. A similar decrease in lesion incidence was noted in female rats exposed to JP-7 vapor sacrificed immediately following exposure. There was a slight increase in C-cell

adenomas in the high concentration JP-7 male rats held postexposure.

Foci of hepatocellular alteration was noted in 15% of the control male rats examined immediately following exposure, but was not seen in control females similarly examined. Female rats exposed to JP-TS and held postexposure had an increased incidence in this lesion while their male counterparts did not. Mononuclear cell leukemia was present only in animals held postexposure (**Tables 15** and **16**). Exposure did not effect the incidence of this neoplasm. The incidence of kidney adenomas in fuel-exposed animals was low, but appeared to be treatment-related.

No adrenal gland tumors occurred in any of the rats examined immediately following exposure termination and hyperplasia was present in only two male rats (one was a control animal and the other a low-concentration JP-7-exposed animal). In all rats held postexposure, pheochromocyte hyperplasia and pheochromocytomas were more common in males than in females. Testicular interstitial cell tumors were commonly found in all male rat groups. Mammary glandular hyperplasia was also commonly seen in exposed male and female animals. The incidence in male rats decreased with exposure. Exposed animals had a higher incidence of fibroadenoma than did their control counterparts. Retinal degeneration, characterized by thinning or complete loss of a nuclear layer, was present in the rat groups maintained one year postexposure.

Hyaline degeneration of the nasal mucosal and submucosal gland epithelium was prevalent in all mouse groups (**Tables 17** through **20**). There was a fairly marked variability between groups and a slightly increased frequency in some exposure groups versus control groups, although no treatment-response relationship was evident. Adrenal capsular cell hyperplasia was present in a high frequency in all female mouse groups, both

those examined immediately following exposure and those held for one-year postexposure. This lesion was less common in male mice. Adrenal cortical hyperplasia was commonly seen in male mice held postexposure.

Granulocytic hyperplasia of the bone marrow was fairly common in all mouse groups and was occasionally associated with inflammation, such as chronic ulcerative dermatitis. This lesion was also commonly observed in all mouse groups without an apparent treatment relationship. Several lesions, lymphoid hyperplasia of the mandibular lymph node and hepatic inflammation, were more frequently observed in the female mouse groups. Glomerulonephritis was diagnosed in all animal groups at the conclusion of the postexposure period.

A high incidence of cataracts was noted in the female mice held postexposure. Also, keratitis was observed at this time point. It should be noted that only if questionable lesions existed were the eyes examined histopathologically. Therefore, the incidence (percent) noted in the tables can be misleading.

Lymphoid hyperplasia and malignant lymphoma of the lymphoreticular organs, and lymphocytic inflammation in nonlymphoid organs such as the salivary gland, liver, lung, and kidney increased with age and was more prevalent in female mice (**Tables 21** through **24**). Pituitary adenomas and hyperplasia were observed at a high frequency in all female mice held for one-year postexposure. Hepatic and pancreatic neoplasms were observed in about the same frequency in all experimental groups, but the incidence was higher in the female mouse groups.

Table 9. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in F-344 Rats Following One-Year Inhalation Exposure to JP-TS Vapor

	Male			Female		
Organ	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Nose:						
Eosinophilic crystals	0	14	7	0	0	0
Inflammation	11	0	11	0	0	6
Liver:						
Bile duct hyperplasia	38	29	57	8	0	8
(severity)[a]	(1.8)	(2.0)	(2.4)	(1.0)	(0.0)	(1.0)
Kidney:						
Renal mineralization	0	0	86[b]	0	0	0
(severity)	(0.0)	(0.0)	(2.2)[b]	(0.0)	(0.0)	(0.0)
Pelvic hyperplasia	0	0	0	0	0	0
Nephropathy	54	0[c]	21	8	0	0
(severity)	(1.1)	(0.0)	(1.3)	(1.0)	(0.0)	(0.0)
Hyaline droplets	100	100	100	0	0	0
Hydronephrosis	0	8	14	0	0	0
(severity)	(0.0)	(0.2)	(0.2)	(0.0)	(0.0)	(0.0)

[a]Mean severity score based on 0 = normal; 1 = minimal; 2 = mild; 3 = moderate; and 4 = severe. Score is the mean score of affected animals.

[b]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.

[c]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.

Table 10. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in F-344 Rats Exposed to JP-TS Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

	Male			Female		
Organ	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Nose:						
Eosinophilic crystals	89	95	87	90	94	87
Inflammation	14	2	34[b]	20	3[c]	0[c]
Liver:						
Bile duct hyperplasia	59	64	69	5	14	13
(severity)[a]	(2.4)	(2.6)	(2.5)	(1.0)	(1.1)	(1.1)
Kidney:						
Renal mineralization	3	1	96[c]	15	7	2[b]
(severity)	(1.0)	(1.0)	(2.7)[c]	(1.3)	(1.0)	(1.0)
Pelvic hyperplasia	7	2[c]	39[c]	0	4	1
Nephropathy	97	94	99	36	12[b]	28
(severity)	(2.1)	(2.5)	(2.6)	(1.2)	(1.6)	(1.4)
Hyaline droplets	100	99	100	0	0	0
Hydronephrosis	15	7	31	0	0	1
(severity)	(0.2)	(0.2)	(0.5)	(0.0)	(0.0)	(0.0)
Eye:						
Retinal degeneration	67	17[c]	7[c]	97	37[c]	29[c]

[a]Mean severity score based on 0 = normal; 1 = minimal; 2 = mild; 3 = moderate; and 4 = severe. Score is the mean score of affected animals.

[b]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.

[c]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.

Table 11. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in F-344 Rats Following One-Year Inhalation Exposure to JP-7 Vapor

	Male			Female		
Organ	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Nose:						
Eosinophilic crystals	0	8	8	0	8	8
Inflammation	11	0	23	0	9	18
Liver:						
Bile duct hyperplasia	38	25	33	8	0	0
(severity)[a]	(1.8)	(1.0)	(1.7)	(1.0)	(0.0)	(0.0)
Kidney:						
Renal mineralization	0	0	0	0	0	0
(severity)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Pelvic hyperplasia	0	0	0	0	0	0
Nephropathy	54	8	50	8	0	0
(severity)	(1.1)	(1.1)	(1.0)	(1.0)	(0.0)	(0.0)
Hyaline droplets	100	100	100	0	0	0
Hydronephrosis	0	25	42	0	0	0
(severity)	(0.0)	(0.5)	(0.5)	(0.0)	(0.0)	(0.0)

[a]Mean severity score based on 0 = normal; 1 = minimal; 2 = mild; 3 = moderate; and 4 = severe. Score is the mean score of affected animals.

Table 12. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in F-344 Rats Exposed to JP-7 Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

	Male			Female		
Organ	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Nose:						
Eosinophilic crystals	89	77	84	90	69[b]	78
Inflammation	14	0[b]	13	20	7	3
Liver:						
Bile duct hyperplasia	59	62	47	5	3	6
(severity)[a]	(2.4)	(2.6)	(2.5)	(1.0)	(1.1)	(1.1)
Kidney:						
Renal mineralization	3	1[c]	77[c]	15	1[c]	1[c]
(severity)	(1.0)	(1.0)	(2.6)	(1.3)	(1.0)	(1.0)
Pelvic hyperplasia	7	5	14	0	0	2
Nephropathy	97	91	98	36	36	10[c]
(severity)	(2.1)	(2.2)	(2.4)	(1.2)	(1.2)	(1.2)
Hyaline droplets	100	100	99	0	3	0
Hydronephrosis	15	24	28	0	0	0
(severity)	(0.2)	(0.4)	(0.5)	(0.0)	(0.0)	(0.0)
Eye:						
Retinal degeneration	67	12[c]	22[c]	97	26[c]	42[c]

[a]Mean severity score based on 0 = normal; 1 = minimal; 2 = mild; 3 = moderate; and 4 = severe. Score is the mean score of affected animals.

[b]Significantly different from control, $p<0.05$, as determined by a *Chi-square test of proportion.*

[c]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.

Table 13. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in F-344 Rats Following One-Year Inhalation Exposure to JP-TS Vapor

	Male			Female		
Organ	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Thyroid:						
C-cell hyperplasia	67	15	8[a]	70	0[a]	45
C-cell adenoma	0	0	0	0	0	0
Liver:						
Foci of hepatocellular alteration	15	0	0	0	8	0

[a]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.

Table 14. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in F-344 Rats Following One-Year Inhalation Exposure to JP-7 Vapor

	Male			Female		
Organ	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Thyroid:						
C-cell hyperplasia	67	64	9	70	25	15
C-cell adenoma	0	9	0	0	12	0
Liver:						
Foci of hepatocellular alteration	15	25	0	0	0	0

Table 15. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in F-344 Rats Exposed to JP-TS Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

Organ	Male			Female		
	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Thyroid:						
C-cell hyperplasia	70	43[a]	36[b]	51	65	78[a]
C-cell adenoma	11	8	7	0	15[a]	4
C-cell carcinoma	0	0	1	0	1	0
Liver:						
Foci of hepatocellular alteration	38	9[b]	5[b]	3	12	19[a]
Spleen:						
Mononuclear cell leukemia	26	19	27	20	16	17
Kidney:						
Renal adenomas	0	0	4[a]	0	0	1
Adrenal:						
Pheochromocyte hyperplasia	15	13	19	2	10	7
Pheochromocytoma	13	13	13	7	2	7
Testes:						
Interstitial cell tumor	92	92	93	---	---	---
Mammary gland:						
Glandular hyperplasia	24	2[b]	10	38	41	44
Fibroadenoma	1	10	10	6	12	13

[a]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.
[b]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.

Table 16. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in F-344 Rats Exposed to JP-7 Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

	Male			Female		
Organ	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Thyroid:						
C-cell hyperplasia	70	60	48	51	69	57
C-cell adenoma	11	12	18	0	6	8
C-cell carcinoma	0	1	0	0	0	1
Liver:						
Foci of hepatocellular alteration	38	26	7[a]	3	5	3
Spleen:						
Mononuclear cell leukemia	26	27	23	20	10	21
Kidney:						
Renal adenomas	0	1	3	0	0	0
Adrenal:						
Pheochromocyte hyperplasia	15	13	15	2	1	4
Pheochromocytoma	13	7	21	7	4	6
Testes:						
Interstitial cell tumor	92	91	90	---	---	---
Mammary gland:						
Glandular hyperplasia	24	13	2[b]	38	36	11[a]
Fibroadenoma	1	8	13	6	17	17

[a]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.
[b]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.

Table 17. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in C57BL/6 Mice Following One-Year Inhalation Exposure to JP-TS Vapor

	Male			Female		
Organ	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Nose:						
Hyaline degeneration	58	53	70	33	29	24
Adrenal:						
Capsular cell hyperplasia	3	0	12	50	93	69
Bone marrow:						
Granulocytic Hyperplasia	20	3	4	8	0	0
Mandibular lymph node						
Lymphoid hyperplasia	0	3	0	33	20	75
Kidney:						
Lymphatic infiltrates	49	22	41	65	81	65
Glomerulo-nephritis	0	0	0	0	0	9
Liver:						
Inflammation	0	0	0	0	44[a]	65[b]

[a]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.
[b]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.

Table 18. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in C57BL/6 Mice Exposed to JP-TS Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

	Male			Female		
Organ	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Nose:						
Hyaline degeneration	81	71	41[a]	45	68	57
Adrenal:						
Capsular cell hyperplasia	23	0[b]	18	81	90	89
Cortical hyperplasia	21	17	31	10	1	11
Bone Marrow:						
Granulocytic hyperplasia	13	31	7	10	16	11
Mandibular Lymph Node:						
Lymphoid hyperplasia	2	11	0	43	61	63
Kidney:						
Lymphocytic infiltrates	78	69	68	75	88	81
Glomerulo-nephritis	18	18	25	15	18	20
Liver:						
Inflammation	0	0	0	8	25[a]	18[a]
Eye:						
Cataracts	100	0	0	85	61	65
Keratitis	11	0	0	34	46	56

[a]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.
[b]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.

Table 19. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in C57BL/6 Mice Following One-Year Inhalation Exposure to JP-7 Vapor

	Male			Female		
Organ	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Nose:						
Hyaline degeneration	58	52	68	33	51	12
Adrenal:						
Capsular cell hyperplasia	3	0	6	50	88[a]	80
Bone marrow:						
Granulocytic Hyperplasia	20	8	10	8	8	6
Mandibular lymph node						
Lymphoid hyperplasia	0	0	0	33	75	69
Kidney:						
Lymphatic infiltrates	49	40	33	65	74	47
Glomerulo-nephritis	0	0	0	0	6	0
Liver:						
Inflammation	0	0	0	0	18	56[b]

[a]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.
[b]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.

Table 20. Incidence (%) Summary of Selected Microscopic Nonneoplastic Lesions in C57BL/6 Mice Exposed to JP-7 Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

	Male			Female		
Organ	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Nose:						
Hyaline degeneration	81	92	78	45	76[b]	65
Adrenal:						
Capsular cell hyperplasia	23	0[a]	10	81	91	92
Cortical hyperplasia	21	47	25	10	2	3
Bone Marrow:						
Granulitic hyperplasia	13	5	7	10	8	14
Mandibular Lymph Node:						
Lymphoid hyperplasia	2	0	3	43	70	45
Kidney:						
Lymphatic infiltrates	78	69	58	75	87	76
Glomerulo-nephritis	18	18	16	15	17	18
Liver:						
Inflammation	0	0	0	8	29[a]	27[a]
Eye:						
Cataracts	100	50	92	85	54[b]	86
Keratitis	11	50	17	34	65	17

[a]Significantly different from control, $p<0.01$, as determined by a Chi-square test of proportion.
[b]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.

Table 21. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in C57BL/6 Mice Following One-Year Inhalation Exposure to JP-TS Vapor

	Male			Female		
Organ or System	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Lymphoreticular: Malignant lymphoma	0	3	3	4	0	0
Pituitary: Adenoma	0	0	0	0	0	0
Liver: Malignant lymphoma	3	0	0	0	0	0
Pancreas: Malignant lymphoma	4	0	0	0	0	0

Table 22. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in C57BL/6 Mice Exposed to JP-TS Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

	Male			Female		
Organ or System	Control	200 mg/m^3	1000 mg/m^3	Control	200 mg/m^3	1000 mg/m^3
Lymphoreticular: Malignant lymphoma	25	25	23	60	35	49
Pituitary: adenoma	0	0	0	54	40	52
Liver: Malignant lymphoma	7	11	11	32	23	22
Pancreas: Malignant lymphoma	0	0	0	5	3	3

Table 23. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in C57BL/6 Mice Following One-Year Inhalation Exposure to JP-7 Vapor

	Male			Female		
Organ or System	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Lymphoreticular: Malignant lymphoma	0	0	4	4	3	0
Pituitary: adenoma	0	0	0	0	4	17
Liver: Malignant lymphoma	3	0	5	0	3	0
Pancreas: Malignant lymphoma	4	0	0	0	0	0

Table 24. Incidence (%) Summary of Hyperplastic and Neoplastic Lesions in C57BL/6 Mice Exposed to JP-7 Vapor that Died Postexposure or Were Sacrificed Following the Postexposure Period

	Male			Female		
Organ or System	Control	150 mg/m^3	750 mg/m^3	Control	150 mg/m^3	750 mg/m^3
Lymphoreticular: Malignant lymphoma	25	23	22	60	29	45
Pituitary: adenoma	0	0	0	54	44	34
Liver: Malignant lymphoma	7	4	8	32	5[a]	22
Pancreas: Malignant lymphoma	0	1	3	5	4	4

[a]Significantly different from control, $p<0.05$, as determined by a Chi-square test of proportion.

SECTION 4

DISCUSSION

Petroleum distillate fuels are used in vast quantities in military aircraft, and as a result, large quantities of distillate fractions have been introduced to the workplace atmosphere. The vaporization procedures used in these studies were designed to produce chamber atmospheres similar to those encountered in field conditions. Generated vapors consisted of hydrocarbon fraction vapors similar to those originating from routine fueling operations or accidental spills. The fuels JP-TS and JP-7 can best be described as middle-distillate fuels. More dense hydrocarbon fractions, which were not readily vaporized at 50 °C, were not significant components of the chamber atmosphere. The residual hydrocarbons, which were discarded as waste, could have contained the more potent carcinogens.

Pathophysiologic changes in rats and mice exposed to JP-TS and JP-7 fuel vapor for one year indicated no significant respiratory toxicity. Except for slightly depressed body weight gains in male rats, both species tolerated the exposures without a concentration-related increase in either morbidity or mortality. Hematologic and clinical chemistry evaluations conducted on rats sacrificed at exposure termination failed to identify changes that were considered to have pathophysiologic significance. Although several parameters were found to be significantly different from control values, all were within the normal range reported by other investigators (Wolford et al., 1986).

Significant microscopic findings following the one-year fuel-inhalation exposure were primarily restricted to renal lesions found in male rats. Medullary and papillary mineralization in the high-concentration JP-TS-exposed male rats

appeared treatment-related for both incidence and severity. Hydronephrosis was also common in all male treatment groups. The incidence was almost doubled in all fuel-exposed groups with the exception of the low-concentration JP-TS group held postexposure. Severity of this lesion was also increased in all affected exposure groups. Progressive rat neuropathy is known to be age related and was evident in this study by comparison of the control animals sacrificed immediately following exposure and those maintained for an additional one-year postexposure period. In males, severity but not incidence, was increased with age. This is best noted in the JP-TS-exposed animals. In an earlier JP-5 study (Gaworski et al., 1985), exposure was found to increase the incidence of this lesion in male rats. Any possible exposure-related change in incidence in this study would have been masked by the high incidence of age-related change. As in the JP-5 study, pelvic hyperplasia was found to be related to mineralization and could be the result of mechanical irritation by mineral debris. Increased severity of progressive rat nephropathy, the presence of tubular mineralization, and urothelial hyperplasia are consistent with changes previously reported in rats treated with JP-5 (Parker et al., 1981; Gaworski et al., 1985) and similar volatile hydrocarbons (Carpenter et al., 1975a, 1975b; Alden et al., 1983).

Hyaline droplets were found in 99% or greater of all male rats examined. Treated rats examined immediately following exposure had larger droplets, and more of them than the corresponding rats examined after the postexposure period. This effect appeared to be treatment-related but not concentration-related, and it lessened as the postexposure time interval increased. A detailed description of the appearance and size change is included with the pathology reports attached as **Appendices G** and **H**.

Eosinophilic crystals were present in the cytoplasm of nasal glandular epithelium. The incidence of these crystals was high

in animals held postexposure but was not treatment-related. Contrary to findings in the earlier JP-5 study (Gaworski et al., 1985), granulocytic hyperplasia and osteosclerosis were rarely diagnosed in animals exposed to JP-TS and JP-7.

Bile duct hyperplasia with periportal fibrosis was commonly seen in male rats, particularly in those held postexposure. The increased incidence seen in these animals was considered to be age-related. Retinal degeneration characterized by thinning or complete loss of a nuclear layer was present in animals held postexposure. Degeneration was more prevalent in controls than in fuel-exposed animals, and in females than in males. The apparent sparing effect seen in exposed males was not understood, nor was the greater incidence in female rats.

No treatment-related neoplastic lesions were observed in the animals examined following the one-year inhalation study.

The increased prevalence of hyaline degeneration of the nasal mucosal and submucosal gland epithelium reported in mice following JP-5 exposure (Gaworski et al., 1985) was not apparent for either of the two fuels tested in this study. Malignant lymphoma, common in the C57BL/6 mouse (Frith et al., 1983), was frequently observed in all experimental groups held for one-year postexposure with no concentration-response relationship. The incidence in this study (60% in female controls) was appreciably greater than reported in the JP-5 study (11.4%) and in the Frith report (36.8%). Neoplasms of the digestive tract were observed in the mouse treatment groups, but with the exception of intestinal adenoma, no more than one neoplasm was diagnosed in a particular segment of the gastrointestinal tract in each experimental group.

Of particular interest was the high incidence of cataracts in female mice and keratitis in all mice held postexposure.

Neither change was mentioned in the JP-5 report, while cataracts were occasionally observed by Frith.

SUMMARY

The most significant findings in these animals were the variety and increased incidence of renal disease in male rats, similar to changes reported with JP-4, JP-5, and other hydrocarbon inhalation exposures. Furthermore, renal neoplasms, though increased only slightly in numbers, were thought to be exposure-related. There was no distinct evidence that exposure to JP-TS or JP-7 vapor resulted in accelerated degenerative changes or increased tumorigenesis in any major mouse organ system.

Appendix A. Comparison of the Five Largest Gas Chromatographic Peaks[a] From Each JP-TS Drum

Peak #	1	2	3	4	5
Peak Retention Time (Min)	21.54	25.91	29.92	22.61	33.67
Drum #					
1	5.82	4.35	2.33	2.12	1.77
2	5.58	4.59	2.40	2.13	1.94
3	5.15	4.29	2.35	1.93	1.88
4	5.60	5.50	2.64	2.08	2.36
5	5.87	4.96	2.60	1.99	1.98
6	5.90	4.45	2.50	2.16	1.86
7	6.07	4.70	2.58	2.20	2.05
8	5.51	5.70	2.91	1.86	2.41
9	5.40	5.17	2.98	2.03	2.81
10	5.24	4.34	2.39	1.95	1.90
11	5.51	4.43	2.51	2.03	2.04
12	5.47	4.31	2.52	2.04	2.03
13	6.18	5.27	2.63	2.32	2.26
14	4.87	4.19	2.38	1.84	1.98
15	4.58	3.88	2.16	1.72	1.85
16	5.86	4.61	2.31	2.22	1.77
17	5.43	4.29	2.27	1.99	1.78
18	5.84	4.90	2.19	2.21	1.65
19	6.18	5.44	2.24	3.02	1.51
20	5.98	5.53	2.32	2.16	2.01
21	4.89	3.81	2.04	1.83	1.58
22	6.23	4.40	2.31	2.25	1.58
23	6.06	4.06	2.17	2.11	1.69
24	6.09	4.49	2.40	2.21	1.78
25	6.22	4.62	2.12	2.31	1.48

[a]Numbers are percent of total area from all gas chromatographic peaks recorded.

Appendix B. Comparison of the Ten Largest Gas Chromatographic Peaks[a] From Each JP-7 Drum

Peak #	1	2	3	4	5	6	7	8	9	10
Peak Retention Time (Min)	21.52	25.88	28.52	29.92	30.53	32.77	33.67	35.93	36.45	37.16
Drum #										
014	1.19	3.00	1.57	5.60	2.78	2.32	5.93	1.65	2.22	3.94
015	0.54	3.20	1.54	5.91	2.88	2.00	6.14	1.56	2.24	3.97
016	1.75	4.30	1.86	7.12	3.40	2.54	7.12	1.54	2.42	4.54
017[b]	1.02	2.70	5.62	5.16	2.33	2.37	4.44	1.95	1.18	2.85
018	1.75	4.34	1.77	6.75	3.32	2.57	7.38	1.60	2.57	4.85
019	1.86	4.32	1.68	7.05	3.50	2.78	7.52	1.54	2.49	4.80
020	1.00	2.89	1.60	5.63	2.75	2.35	5.79	1.59	2.16	3.71
021	1.68	4.27	1.47	6.68	3.32	2.59	7.45	1.65	2.61	4.96
022	1.27	3.07	1.65	5.59	2.73	2.13	5.60	1.46	2.07	3.59
023	1.76	4.13	1.85	7.18	3.36	2.62	6.92	1.48	2.39	4.69
024	1.81	4.26	1.92	7.40	3.53	2.73	7.33	1.46	2.39	4.60
025	1.42	3.46	1.70	6.30	3.07	2.51	6.40	1.47	2.13	3.89
026	1.12	3.96	1.62	5.62	2.75	2.33	5.67	1.51	2.12	3.67
027	1.17	2.96	1.60	5.52	2.68	2.26	5.51	1.49	2.03	3.66
028	1.10	2.97	1.59	5.20	2.23	2.23	5.47	1.51	2.03	3.47
029	1.79	4.17	1.86	7.18	3.39	2.56	7.38	1.58	2.53	4.17
030	1.21	3.06	1.58	5.57	2.73	2.32	5.67	1.53	2.13	3.74
031	1.81	4.34	0.99	7.08	3.46	2.56	7.33	1.52	2.42	4.63
032	1.20	2.96	1.59	5.57	2.70	2.30	5.64	1.56	2.13	3.72
033	1.45	3.36	1.69	6.49	3.13	2.66	6.66	1.56	2.27	4.12
034	1.26	3.02	1.60	5.54	2.74	2.26	5.63	1.53	2.10	3.62
035	1.89	4.49	1.87	7.09	3.46	2.70	7.46	1.56	2.55	4.95
036	1.13	2.83	1.55	4.96	2.60	2.20	5.28	1.47	2.00	3.54
037	1.52	4.06	1.76	6.40	3.28	2.81	7.45	1.56	2.39	4.49
038	1.75	4.29	1.82	6.64	3.36	2.76	7.60	1.50	2.47	4.91

[a] Numbers are percent of total area from all gas chromatographic peaks recorded.
[b] Fuel not used in this study.

Appendix C. Body Weights[a] (g) of Male F-344 Rats Following One-Year Repeated Inhalation Exposure to JP-TS Fuel

Week	Control	200 mg/m^3	1000 mg/m^3
-2	188 ± 1	188 ± 1	190 ± 1
0	216 ± 1	215 ± 1	210 ± 2[b]
2	235 ± 1	240 ± 2[b]	240 ± 2[b]
4	253 ± 2	246 ± 2[b]	251 ± 2
6	270 ± 1	253 ± 2[b]	258 ± 1[b]
8	273 ± 1	271 ± 2	272 ± 1
10	291 ± 2	280 ± 2[b]	283 ± 2[b]
12	297 ± 2	286 ± 2[b]	290 ± 2[b]
14	304 ± 2	293 ± 2[b]	298 ± 2[b]
16	311 ± 2	299 ± 2[b]	307 ± 2[b]
18	316 ± 2	305 ± 2[b]	312 ± 2[b]
20	327 ± 2	307 ± 3[b]	322 ± 2[b]
22	310 ± 2	295 ± 2[b]	303 ± 2[b]
24	323 ± 2	305 ± 3[b]	324 ± 2
26	342 ± 2	317 ± 4[b]	334 ± 2[b]
28	347 ± 2	334 ± 2[b]	341 ± 2[b]
30	351 ± 2	344 ± 2[b]	345 ± 3[b]
32	360 ± 2	342 ± 3[b]	357 ± 2[c]
34	366 ± 2	340 ± 3[b]	359 ± 2[b]
36	374 ± 2	360 ± 3[b]	372 ± 3
38	378 ± 2	365 ± 2[b]	369 ± 3[b]
40	381 ± 2	372 ± 2[b]	376 ± 2[b]
42	384 ± 2	380 ± 2[b]	382 ± 2
44	392 ± 2	381 ± 3[b]	389 ± 2
46	393 ± 2	384 ± 2[b]	394 ± 3
48	403 ± 2	392 ± 3[b]	401 ± 3
50	403 ± 2	394 ± 3[b]	399 ± 3[b]
52	405 ± 2	396 ± 3[b]	408 ± 3[b]
56	421 ± 3	412 ± 3[b]	412 ± 3[b]
60	429 ± 3	423 ± 3[b]	422 ± 3[b]
64	439 ± 3	435 ± 3[c]	427 ± 3[b]
68	443 ± 3	438 ± 3[b]	431 ± 3[b]
72	444 ± 3	438 ± 3[b]	433 ± 3[b]
76	439 ± 3	437 ± 3	428 ± 3[b]
80	437 ± 3	435 ± 3	425 ± 3[b]
84	449 ± 3	431 ± 3[b]	422 ± 3[b]
88	444 ± 3	425 ± 4[b]	416 ± 3[b]
92	437 ± 3	427 ± 4[b]	421 ± 3[b]
96	437 ± 3	417 ± 3[b]	403 ± 4[b]

[a] Mean + SEM with 60-100 (control), 62-100 (200 mg/m^3) n = 64-100 (1000mg/m^3).

[b] Significantly different from control group at $p<0.01$ as determined by analysis of variance with Scheffe multiple comparisons.

[c] Significantly different from control group at $p<0.05$ as determined by analysis of variance with Scheffe multiple comparisons.

Appendix D. Body Weights[a] (g) of Female F-344 Rats Following One-Year Repeated Inhalation Exposure to JP-TS Fuel

Week	Control	200 mg/m^3	1000 mg/m^3
-2	130 ± 1	131 ± 1	130 ± 1
0	141 ± 1	145 ± 1[b]	145 ± 2[b]
2	153 ± 1	161 ± 1[b]	158 ± 1[b]
4	160 ± 1	169 ± 1[b]	166 ± 1[b]
6	164 ± 1	171 ± 1[b]	168 ± 1[b]
8	166 ± 1	179 ± 1[b]	173 ± 1[b]
10	171 ± 1	183 ± 1[b]	179 ± 1[b]
12	178 ± 1	185 ± 1[b]	179 ± 1
14	180 ± 1	185 ± 1[b]	181 ± 1
16	181 ± 1	187 ± 1[b]	184 ± 1
18	181 ± 1	189 ± 1[b]	186 ± 1[b]
20	182 ± 1	191 ± 1[b]	188 ± 1[b]
22	183 ± 1	188 ± 1[b]	186 ± 1[b]
24	182 ± 1	195 ± 1[b]	190 ± 1[b]
26	187 ± 1	199 ± 1[b]	192 ± 1[b]
28	189 ± 1	201 ± 1[b]	196 ± 1[b]
30	188 ± 1	200 ± 1[b]	198 ± 1[b]
32	190 ± 1	199 ± 1[b]	197 ± 1[b]
34	195 ± 1	200 ± 1[b]	198 ± 1[b]
36	194 ± 1	201 ± 1[b]	200 ± 1[b]
38	198 ± 1	204 ± 1[b]	200 ± 1
40	202 ± 1	210 ± 1[b]	202 ± 1
42	204 ± 1	209 ± 1[b]	203 ± 1
44	206 ± 1	208 ± 1	206 ± 1
46	208 ± 1	206 ± 1	208 ± 1
48	211 ± 1	208 ± 1[c]	210 ± 1
50	212 ± 1	208 ± 1[b]	209 ± 1[c]
52	209 ± 1	212 ± 1[c]	211 ± 1
56	215 ± 1	214 ± 1	213 ± 1
60	219 ± 1	221 ± 1	222 ± 1[b]
64	224 ± 1	230 ± 2[b]	228 ± 2[b]
68	232 ± 2	235 ± 2	235 ± 2
72	237 ± 2	242 ± 2[b]	242 ± 2[b]
76	242 ± 2	246 ± 2[b]	250 ± 2[b]
80	243 ± 2	249 ± 2[b]	253 ± 2[b]
84	252 ± 2	251 ± 2	255 ± 2
88	255 ± 2	254 ± 2	253 ± 3
92	258 ± 3	261 ± 2[c]	268 ± 3[b]
96	267 ± 2	262 ± 2[b]	269 ± 3

[a] Mean ± SEM with n = 64-100 (control), n = 73-100 (200mg/m^3), n = 70-100 (1000mg/m^3)

[b] Significantly different from control group at $p<0.01$ as determined by analysis of variance with Scheffe multiple comparisons.

[c] Significantly different from control group at $p<0.05$ as determined by analysis of variance with Scheffe multiple comparisons.

Appendix E. Body Weights[a] (g) of Male F-344 Rats Following One-Year Repeated Inhalation Exposure to JP-7 Fuel

Week	Control	150 mg/m^3	750 mg/m^3
-2	188 ± 1	190 ± 1	189 ± 1
0	216 ± 1	219 ± 1[b]	214 ± 1
2	235 ± 1	238 ± 1[c]	233 ± 1
4	253 ± 2	259 ± 1[c]	252 ± 1
6	270 ± 1	270 ± 1	256 ± 2[c]
8	273 ± 1	283 ± 1[c]	266 ± 2[c]
10	291 ± 2	289 ± 1	277 ± 2[c]
12	297 ± 2	294 ± 2[c]	285 ± 2[c]
14	304 ± 2	303 ± 2	294 ± 2[c]
16	311 ± 2	311 ± 2	303 ± 2[c]
18	316 ± 2	315 ± 2	310 ± 2[c]
20	327 ± 2	325 ± 2	317 ± 2[c]
22	310 ± 2	312 ± 2	304 ± 2[c]
24	323 ± 2	330 ± 2[c]	324 ± 2
26	342 ± 2	339 ± 2[c]	331 ± 2[c]
28	347 ± 2	348 ± 2	342 ± 2[c]
30	351 ± 2	359 ± 2[c]	349 ± 2
32	360 ± 2	361 ± 2	352 ± 2[c]
34	366 ± 2	366 ± 2	353 ± 3[c]
36	374 ± 2	370 ± 2	360 ± 3[c]
38	378 ± 2	375 ± 2	365 ± 3[c]
40	381 ± 2	380 ± 2	379 ± 3
42	384 ± 2	381 ± 2[c]	381 ± 3[c]
44	392 ± 2	390 ± 2	383 ± 3[c]
46	393 ± 2	390 ± 2	382 ± 3[c]
48	403 ± 2	395 ± 2[c]	387 ± 3[c]
50	403 ± 2	401 ± 2	389 ± 3[c]
52	405 ± 2	401 ± 2[b]	395 ± 3[c]
56	421 ± 3	423 ± 2	415 ± 3[c]
60	429 ± 3	433 ± 2[c]	423 ± 3[c]
64	439 ± 3	442 ± 2	431 ± 3[c]
68	443 ± 3	448 ± 2[c]	439 ± 3[c]
72	444 ± 3	451 ± 3[c]	441 ± 3
76	439 ± 3	449 ± 3[c]	439 ± 3
80	437 ± 3	446 ± 3[c]	438 ± 3
84	449 ± 3	451 ± 4	444 ± 3[c]
88	444 ± 3	449 ± 3[c]	437 ± 4[c]
92	437 ± 3	443 ± 4[c]	432 ± 4[c]
96	437 ± 3	436 ± 5	432 ± 3[c]

[a] Mean ± SEM with N=60-100 (control), N=58-100 (150 mg/m^3 and 750 mg/m^3).

[b] Significantly different from control group at $p<0.05$ as determined by analysis of variance with Scheffe multiple comparisons.

[c] Significantly different from control group at $p<0.01$ as determined by analysis of variance with Scheffe multiple comparisons.

Appendix F. Body Weights[a] (g) of Female F-344 Rats Following One-Year Repeated Inhalation Exposure to JP-7 Fuel

Week	Control	150 mg/m^3	750 mg/m^3
-2	130 ± 1	130 ± 1	132 ± 1
0	141 ± 1	148 ± 1[c]	149 ± 1[c]
2	153 ± 1	162 ± 1[c]	160 ± 1[c]
4	160 ± 1	167 ± 1[c]	167 ± 1[c]
6	164 ± 1	173 ± 1[c]	167 ± 1[b]
8	166 ± 1	179 ± 1[c]	173 ± 1[c]
10	171 ± 1	182 ± 1[c]	177 ± 1[c]
12	178 ± 1	188 ± 1[c]	180 ± 1
14	180 ± 1	189 ± 1[c]	184 ± 1[c]
16	181 ± 1	190 ± 1[c]	188 ± 1[c]
18	181 ± 1	195 ± 1[c]	191 ± 1[c]
20	182 ± 1	196 ± 1[c]	192 ± 1[c]
22	183 ± 1	192 ± 1[c]	189 ± 1[c]
24	182 ± 1	199 ± 1[c]	193 ± 1[c]
26	187 ± 1	199 ± 1[c]	196 ± 1[c]
28	189 ± 1	202 ± 1[c]	201 ± 1[c]
30	188 ± 1	204 ± 1[c]	205 ± 1[c]
32	190 ± 1	203 ± 1[c]	202 ± 1[c]
34	195 ± 1	203 ± 1[c]	196 ± 1
36	194 ± 1	206 ± 1[c]	199 ± 1[c]
38	198 ± 1	208 ± 1[c]	204 ± 1[c]
40	202 ± 1	212 ± 1[c]	211 ± 1[c]
42	204 ± 1	210 ± 1[c]	220 ± 8[c]
44	206 ± 1	211 ± 1[c]	212 ± 1[c]
46	208 ± 1	216 ± 2[c]	209 ± 1
48	211 ± 1	218 ± 1[c]	210 ± 1
50	212 ± 1	217 ± 1[c]	209 ± 1
52	209 ± 1	213 ± 1[c]	208 ± 1
56	215 ± 1	220 ± 1[c]	214 ± 1
60	218 ± 1	224 ± 1[c]	221 ± 1
64	224 ± 1	230 ± 1[c]	227 ± 1[b]
68	232 ± 2	240 ± 2[c]	237 ± 2[c]
72	237 ± 2	248 ± 2[c]	246 ± 2[c]
76	242 ± 2	252 ± 2[c]	251 ± 2[c]
80	243 ± 2	254 ± 2[c]	254 ± 2[c]
84	252 ± 2	264 ± 2[c]	259 ± 2[c]
88	255 ± 2	267 ± 2[c]	264 ± 2[c]
92	258 ± 3	271 ± 2[c]	270 ± 3[c]
96	267 ± 2	271 ± 3[c]	271 ± 3[c]

[a] Mean ± SEM with N=64-100 (control), N=73-100 (150 mg/m^3), 66-100 (750 mg/m^3).

[b] Significantly different from control group at $p<0.05$ as determined by analysis of variance with Scheffe multiple comparisons.

[c] Significantly different from control group at $p<0.01$ as determined by analysis of variance with Scheffe multiple comparisons.

Appendix G. Pathologic Findings in Male and Female F-344 Rats Exposed to JP-TS and JP-7 Vapors for One Year and Held for One-Year Postexposure

HISTOPATHOLOGY SUMMARY OF NON-NEOPLASTIC LESIONS

AAMRL PROJECT: 601-605

1. NOSE: Eosinophilic crystals were present in the cytoplasm of nasal glandular epithelium. These crystals were most common in the nasal sections that contained eyes and harderian glands. The incidence of these crystals was very high in all chronic animals, however, a direct dose effect was not present. Nasal sections from acute animals rarely contained eyes or harderian glands.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Crystals					
% Incidence:					
Acute animals	0 : 0	8 : 8	8 : 8	7 : 0	14 : 0
Chronic animals	89 : 90	77 : 69	84 : 78	95 : 94	87 : 87

2. BONE: Focal, often cystic, chondromucoid degeneration was present in the articular cartilages of the sternum. An apparent male/female incidence difference decreased with age and exposure. Exposure decreased severity in acute males exposed to JP-TS. The incidence in chronic control females approached that in their male counterparts.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Chondromucoid degeneration					
% Incidence:					
Acute animals	92 : 42	91 : 67	82 : 55	46 : 50	62 : 46
Chronic animals	95 : 79	97 : 91	95 : 88	83 : 81	91 : 92

3. BONE MARROW: Contrary to findings in the earlier JP-5 study, granulocytic hyperplasia and osteosclerosis were rarely diagnosed in animals exposed to JP-7 or JP-TS.

4. THYROID: Information on C-cell hyperplasia is presented with data on C-cell neoplasia.

5. HEART: Myocardial fibrosis, acute and chronic inflammation, and myocardial degeneration when combined, were relatively common, although not necessarily drug related. Similar changes have been described in other strains of rats. These changes are reported to be more frequent, to occur

earlier, and to be more severe in males. The apparent sparing effect in high dose-exposed male rats in this study was not clearly understood, neither was the increased incidence in chronic females recieving JP-TS.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
% Incidence:					
Acute	46 : 8	42 : 15	33 : 0	36 : 15	0 : 15
Chronic	46 : 26	48 : 18	38 : 17	37 : 36	20 : 38

6. LIVER:

a. Bile duct hyperplasia with periportal fibrosis was commonly seen in males, especially in chronic groups. The incidence, though low in females, almost tripled in chronic high dose JP-TS exposed females when compared to aged controls. Acute male animals had an incidence of only 25-83% of their chronic counterparts. Also, the severity of this lesion was less in acute animals. Bile duct hyperplasia in aged rats is regarded as relatively insignificant in BN/Bij, WAG/Rij and their (WAGxBN), F_1 hybrid. In F 344 rats, this lesion has been reported to reach an incidence of 98% in 18 month old males. The increased incidence and severity of bile duct hyperplasia and fibrosis seen in our chronic males are thought to be primarily age related.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Bile duct hyperplasia					
% Incidence:					
Acute animals	38 : 8	25 : 0	33 : 0	29 : 0	57 : 8
Chronic animals	59 : 5	62 : 3	47 : 6	64 : 14	69 : 13
Severity:					
Acute animals	1.8 : 1.0	1.0 : 0.0	1.7 : 0.0	2.0 : 0.0	2.4 : 1.0
Chronic animals	2.4 : 1.0	2.3 : 1.7	2.3 : 1.2	2.6 : 1.1	2.5 : 1.1

b. Data concerning foci of cellular alterations is presented with neoplatic lesions.

7. SPLEEN: Hemosiderosis was common in all groups. Severity was lower in exposed females, but incidence was unaffected. Hemosiderosis was usually less severe in animals with mononuclear cell leukemia (MCL). It may be that macrophages which normally phagocytize this pigment are being replaced, or are widely dispersed, by neoplastic cells which almost entirely efface the normal architecture of the spleen. Therefore, the apparent decrease in severity of hemosiderosis in spleens with MCL may be real or relative.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Hemosiderosis					
% Incidence:	93 : 79	75 : 85	93 : 73	71 : 71	70 : 81
Severity:					
Overall	2.3 : 2.6	2.0 : 2.5	2.3 : 2.1	2.1 : 2.0	2.1 : 1.9
MCL absent	2.5 : 2.4	2.0 : 2.6	2.2 : 2.2	2.1 : 2.1	2.1 : 2.0
MCL present	2.2 : 1.5	1.7 : 1.3	2.3 : 1.0	2.0 : 0.0	1.5 : 0.0

8. THYMUS: There was a possible dose related increase in incidence of thymic atrophy in both JP-7 and JP-TS exposed acute exposed males. This was best seen in JP-TS animals. The only group of acute females to have thymic atrophy were the high dose JP-TS animals. There was no apparent difference between chronic males and females.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Thymic atrophy					
% Incidence:					
Acute animals	10 : 0	0 : 0	14 : 0	25 : 0	33 : 17
Chronic animals	81 : 82	74 : 86	93 : 72	88 : 82	87 : 74

9. KIDNEY:

a. Medullary and papillary mineralization. In acute and chronic male groups, this lesion was both exposed and dose related for incidence and for severity. High dose acute JP-TS exposed male animals had lesions, while their counterparts treated with JP-7 (603 group) did not.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Renal mineralization					
% Incidence:					
Acute animals	0 : 0	0 : 0	0 : 0	0 : 0	86 : 0
Chronic animals	3 : 15	1 : 1	77 : 1	1 : 7	96 : 2
Severity:					
Acute animals	0.0 : 0.0	0.0 : 0.0	0.0 : 0.0	0.0 : 0.0	2.2 : 0.0
Chronic animals	1.0 : 1.3	1.0 : 1.0	2.6 : 1.0	1.0 : 1.0	2.7 : 1.0

b. Pelvic Hyperplasia. Focal epithelial hyperplasia occurred primarily in male rats where it was dose related for incidence but not for severity. There is good correlation between this lesion and papillary and medullary mineralization in the present study, as well as in an earlier JP-5 study. It should be noted that though mineralization was present in 86% of acute high

dose (605) males, pelvic hyperplasia was not present in those same animals. Thus, pelvic hyperplasia may be related to the occurrence of medullary mineralization and to the duration where such mineralization is present.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Pelvic hyperplasia					
% Incidence:					
Acute animals	0 : 0	0 : 0	0 : 0	0 : 0	0 : 0
Chronic animals	7 : 0	5 : 0	14 : 2	2 : 4	39 : 1

c. Progressive Rat Nephropathy. This lesion is known to be age related, and this is clearly evident in the present study by comparison of the incidences for acute and chronic controls. In males, severity, but not incidence, was drastically increased by exposure. This is best seen in JP-TS exposed animals. In an earlier JP-5 study, exposure to jet fuel was found to increase the incidence of this lesion in male rats. Any possible exposure-related change in incidence in the present study would have been masked by the high incidence of age-related change. As in the JP-5 study, pelvic hyperplasia was found to be related to mineralization and could be the result of mechanical irritation by mineral debris. Increased severity of progressive rat nephropathy, the presence of tubular mineralization and urothelial hyperplasia are consistent with changes previously reported in rats treated with JP-5, RJ-5, JP-10, tetrachloroethylene and dimethylphosphonate.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Rat nephropathy					
% Incidence:					
Acute animals	54 : 8	8 : 0	50 : 0	0 : 0	21 : 0
Chronic animals	97 : 36	91 : 36	98 : 10	94 : 12	99 : 28
Severity:					
Acute	1.1 : 1.0	1.1 : 0.0	1.0 : 0.0	0.0 : 0.0	1.3 : 0.0
Chronic	2.1 : 1.2	2.2 : 1.2	2.4 : 1.2	2.5 : 1.6	2.6 : 1.4

d. Hydronephrosis. Hydronephrosis occurred primarily in males with a single case in a female. The incidence almost doubled in all exposure groups except chronic 604 animals. Severity was increased in all affected exposure groups. The incidence of hydronephrosis in rats is reported to be strain and sex related.

e. Hyaline Droplets. The incidence of hyaline droplets in sections stained with hematoxylin and eosin ranged from 36-92% in acute animals and from 84-100% in chronic animals. In an effort to more easily see and evaluate hyaline droplets in proximal tubular epithelium, additional kidney sections from each male rat were stained and examined with Mallory Heidenhain's stain. This stain was recommended to us by Dr. Carl L. Alden of the Proctor and Gamble Company, Cincinnati, Ohio. With this stain the incidence of hyaline

droplets was found to range from 99-100%. Using Mallory Heidenhain's stain each kidney section was scored for severity (the numbers of droplets with scores from 0 to 4+); droplet distribution (focal, multifocal, or diffuse; and droplet size (primarily small 5.0, primarily large 10.0, or some combination of the two based on a percentage).

(1) Key findings:

(a) In unexposed controls (601), age had no affect on any of the scored parameters.

(b) In exposed acute animals, droplet severity was slightly less than that of controls (except 602s).

(c) In exposed animals, droplet size was affected by exposure, but was not dose related at the dose levels tested. Droplets in unexposed acute animals were amorphous and $\leq$ 1 µm in diameter; those in exposed acute animals were $\geq$ 2 µm in diameter and crystalloid in appearance. Chronic exposed animals had a combination of these two types.

(d) In exposed chronic animals, severity was less than that of age matched controls.

(e) In exposed chronic animals droplet size was affected by exposure. The mean size of these droplets was larger than that in controls, but was closer to controls than was the mean size of exposed acute animals.

(f) Distribtuion of droplets was primarily diffuse in all groups, except in 605 chronic animals, where it was primarily multifocal. No explanation for this was readily apparent.

(2) Conclusions: Exposed acute animals had larger droplets, and more of them than their corresponding chronic counterparts; this effect, though treatment related, was not dose related, and it lessened as the post-exposure time interval increased. Droplets not only got larger with treatment, they changed in appearance. Either the material in these droplets changed, or the processing of this material by the tubular epithelial cells changed. Some investigators have suggested the material in the large droplets is alpha 2µ globulin and that in the smaller droplets is albumin or some other protein. It is possible both droplets contain alpha 2µ globulin, but are the result of differences in processing of this protein. Sections of two-month-old male quality control rat kidneys were positive for small droplets similar to those seen in the present study. Renal sections from female rats stain similarly to those from the young quality control male rats, and therefore, the material in the small droplets is not thought to be alpha 2µ globulin.

AAMRL Project Summary: Non-Neoplastic Lesions

HEMATOXYLIN AND RESIN STAIN

	601 M	602 M	603 M	604 M	605 M
% Droplet incidence:					
Acute animals	92	58	83	50	36
Chronic animals	100	95	94	95	84

MALLORY HEIDENHAIN'S STAIN

% Droplet incidence:					
Acute animals	100	100	100	100	100
Chronic animals	100	100	99	99	100

HYALINE DROPLETS - KIDNEYS, MALE RATS*

1. ACUTE ANIMALS:

GROUP	SEVERITY	DISTRIBUTION F	DISTRIBUTION MF	DISTRIBUTION D	DROPLET SIZE
601	3.3 + 0.48	100%			5.0 + 0
602	3.4 + 0.51	100%			8.1 + 1.90
603	2.8 + 0.58	100%			10.0 + 0
604	2.5 + 0.65		7%	93%	10.0 + 0
605	2.9 + 0.73		7%	93%	9.8 + 0.67

2. CHRONIC ANIMALS:

GROUP	SEVERITY	DISTRIBUTION F	DISTRIBUTION MF	DISTRIBUTION D	DROPLET SIZE
601	3.3 + 0.98	<<	1%	99%	5.3 + 0.98
602	2.2 + 0.90	5%	13%	82%	6.3 + 1.99
603	1.8 + 0.87	<<	26%	74%	6.6 + 2.20
604	1.7 + 0.80	<<	32%	68%	6.3 + 2.07
605	1.3 + 0.58	1%	63%	36%	8.0 + 2.23

*NOTES:

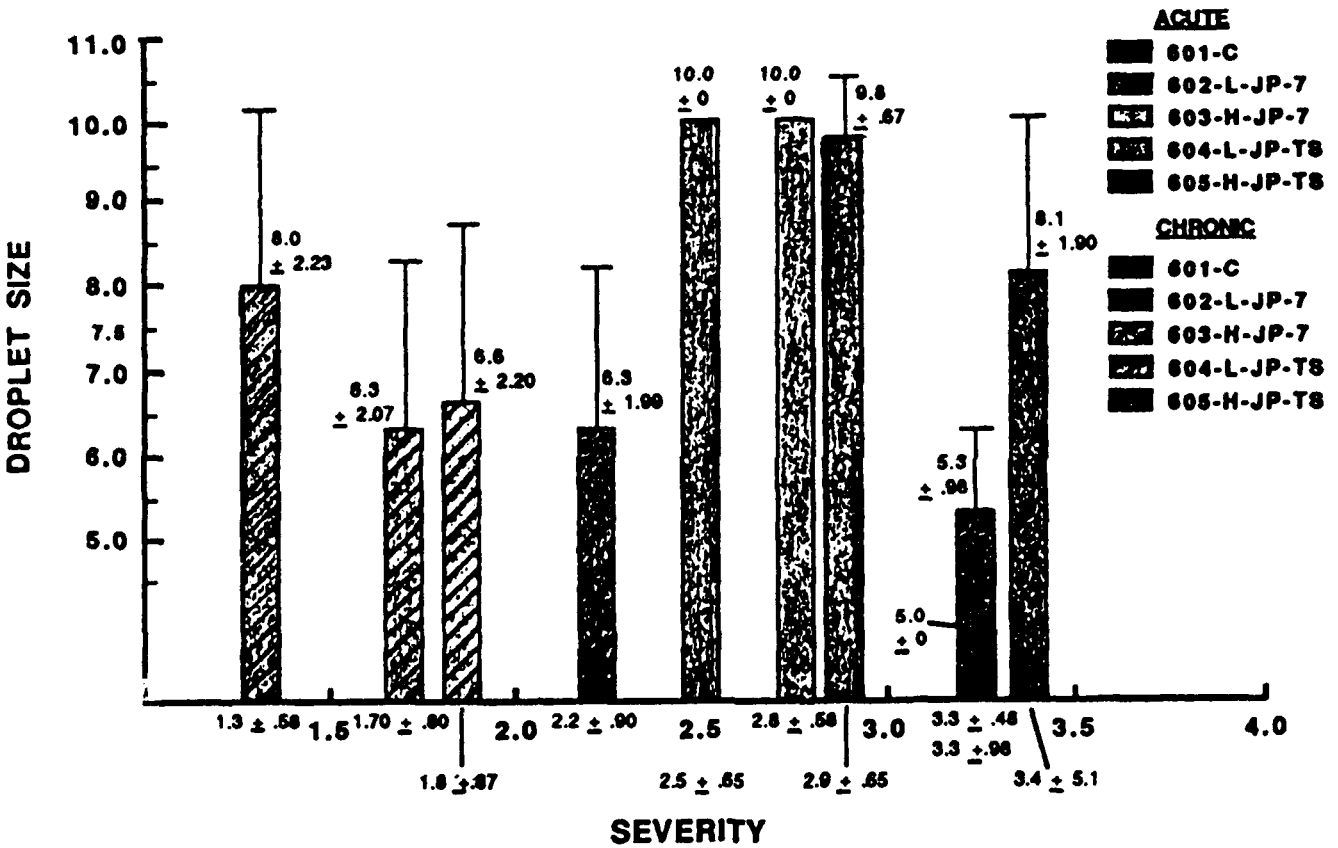
a. Severity scored as: 0 to 4+

b. Distribution given as percentage of total animals in the group:

F = focal; MF = multifocal; D = diffuse

c. Droplet size scored as:

Primarily Small:	5.0
90% Small / 10% Large:	5.5
80% " / 20% " :	6.0
70% " / 30% " :	6.5
60% " / 40% " :	7.0
50% " / 50% " :	7.5
40% " / 60% " :	8.0
30% " / 70% " :	8.5
20% " / 80% " :	9.0
10% " / 90% " :	9.5
Primarily Large:	10.0


DROPLET SIZE
11.0
10.0
9.0
8.0
7.5
7.0
6.0
5.0
8.0 ± 2.23
6.3 ± 2.07
6.6 ± 2.20
6.3 ± 1.00
10.0 ± 0
10.0 ± 0
9.8 ± .67
5.3 ± .96
5.0 ± 0
8.1 ± 1.90
1.3 ± .58
1.5
1.70 ± .80
1.8 ± .87
2.0
2.2 ± .90
2.5
2.5 ± .65
2.8 ± .58
2.9 ± .65
3.0
3.3 ± .48
3.3 ± .96
3.4 ± 5.1
3.5
4.0
SEVERITY
ACUTE
601-C
602-L-JP-7
603-H-JP-7
604-L-JP-TS
605-H-JP-TS
CHRONIC
601-C
602-L-JP-7
603-H-JP-7
604-L-JP-TS
605-H-JP-TS

f. Tubular Pigment. The incidence of tubular pigment was more than 90% in chronic males and females. Neither of these lesions were affected by exposure or by the occurrence of other renal lesions.

10. ADRENAL GLAND: Data on hyperplasia of the cortex and medulla are presented in the section on neoplasms.

11. MAMMARY GLAND: Data on hyperplasia and ductal ectasia are presented in the section on neoplasms.

12. BRAIN: Clear, oval, empty vacuoles were commonly seen in the white matter of the cerebellum, pons and midbrain of chronic animals and less frequently in acute animals. This change has been previously designated vacuolar encephalopathy. These vacuoles do not stain, nor are they associated with reactive gliosis. The incidence of this change increased moderately in exposed females. Similar changes, much more infrequent and less severe, are seen during routine examination of brains from rats 2-6 months old.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
% Incidence:					
Acute animals	17 : 10	27 : 27	17 : 69	0 : 17	21 : 23
Chronic animals	51 : 56	39 : 64	37 : 72	41 : 87	55 : 71

13. EYES: Retinal degeneration characterized by thinning or complete loss of a nuclear layer was present in chronic animals. Sections of eyes from acute animals were not always available for examination. Degeneration was more prevalent in controls than in exposed animals and in females than in males. The apparent sparing effect seen in exposed animals was not understood, neither was the greater incidence in females.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Retinal degeneration					
% Incidence:	67 : 97	12 : 26	22 : 42	17 : 37	7 : 29

HISTOPATHOLOGY SUMMARY OF HYPERPLASTIC AND NEOPLASTIC LESIONS

AAMRL PROJECT: 601-605

(Treatment vs Exposure)

1. THYROID: C-cell hyperplasia was present in more than 50% of male and female controls. A dose related drop in incidence occurred in acute and chronic males. This drop was best appreciated in acute animals. In acute females, a similar drop in incidence occurred in JP-7 exposed females. A drop in incidence occured in JP-TS exposed acute females, but was clearly not dose related. Exposure did not result in a decline in C-cell hyperplasia in chronically exposed females. An apparent dose related increase in the incidence of this lesion in JP-TS chronic females is thought to be spurious. Overall, the incidence of tumors of the thyroid was not significantly affected by exposure. There was, however, a slight increase in adenomas in high dose JP-7 exposed males. Because of the difficulty in separating C-cell hyperplasia from C-cell adenomas, lumping these two lesions may be justified.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
C-Cell Hyperplasia					
% Incidence:					
Acute animals	67 : 70	64 :25	9 : 15	15 : 0	8 : 45
Chronic animals	70 : 51	60 :69	48 : 57	43 : 65	36 : 78
C-Cell Adenoma					
% Incidence:					
Acute animals	0 : 0	9 : 12	0 : 0	0 : 0	0 : 0
Chronic animals	11 : 0	12 : 6	18 : 8	8 : 15	7 : 4
C-Cell Carcinoma					
% Incidence:					
Acute animals	0 : 0	0 : 0	0 : 0	0 : 0	0 : 0
Chronic animals	0 : 0	1 : 0	0 : 1	0 : 1	1 : 0

2. LIVER: Foci of cellular alteration, combined basophilic eosinophilic and clear cell, were age-dependent lesions. Exposed males had fewer of these lesions, while their female counterparts exposed to JP-TS had an increased incidence. The low incidence of this lesion was unexpected, especially in light of the high incidence seen in an earlier JP-5 study. In that earlier study, the incidence was 45% in controls, 70% in low dose animals and 61% in high dose animals. It should be noted in the present study that 1-2 mm foci of tan nodules were reportedly seen grossly in many animals, but were never appreciated microscopically. The nature of these supposed nodules was not determined by us.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Foci of Hepatocellular Alteration					
% Incidence:					
Acute animals	15 : 0	25 : 0	0 : 0	0 : 8	0 : 0
Chronic animals	38 : 3	26 : 5	7 : 3	9 : 12	5 : 19

3. SPLEEN: Mononuclear cell leukemia was present only in chronic animals. Exposure did not affect the incidence of this neoplasm or its pattern of metastasis. The 50% drop in incidence seen in exposed animals in the previous JP-5 study was not seen with JP-7 or JP-TS.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Mononuclear cell leukemia					
% Incidence:					
Chronic animals	26 : 20	27 : 10	23 : 21	19 :16	27 : 17

4. KIDNEY: The incidence of adenoma in exposed animals was low, however, the incidence did appear to be dose related. This trend was best observed in high dose animals (3% for JP-7 and 4% for JP-Ts). This change was considered significant when compared to historical data reporting an incidence rate for renal tumors of less than 1%. Also, renal tumors were not present in any of the other acute animals or in chronic controls. Other jet fuels (RJ-5 and JP-10) have been reported to cause an incidence of renal tumors (combined adenomas and carcinomas) of 13-18% in male rats.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
Renal Adenomas					
% Incidence:					
Chronic animals	0 : 0	1 : 0	3 : 0	0 : 0	4 : 1

5. ADRENAL GLAND: No tumors occurred in any acute animals, and hyperplasia was present in only two acute males (one was a control animal and the other a low dose JP-7 exposed animal). In all chronic groups, pheochromocyte hyperplasia and pheochromocytomas were more common in males than in females. Although pheochromocyte hyperplasia was not dose related in JP-7 high dose exposed males, the incidence of pheochromocytoma in those animals increased by more than 50% in the high dose group. Cortical hyperplasia and adenomas were unaffected by exposure.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
% Incidence chronic animals					
Pheochromocyte hyperplasia:	15 : 2	13 : 1	15 : 4	13 : 10	19 : 7
Pheochromocytoma:	13 : 7	7 : 4	21 : 6	13 : 2	13 : 7

6. TESTES: Testicular interstitial cell tumor is a common age-related neoplasm in F-344 male rats. Exposure did not affect the incidence of this tumor in any of the groups.

	601	602	603	604	605
Interstitial Cell Tumor					
% Incidence chronic animals:	92	91	90	92	93

7. MAMMARY GLAND: No consideration of lesions present in acute animals was possible, because so few mammary glands were submitted from these animals. Glandular hyperplasia was commonly seen in exposed animals (male and female). The incidence in males seemed to be drug related in that it clearly decreased with exposure. A much higher incidence of hyperplasia was seen in JP-7 and JP-TS exposed animals than those exposed to JP-5 study. Our diagnosis of hyperplasia closely followed the interpretations and illustrations of Dr. Joe Burek in his book, Pathology of Aging Rats. Exposed animals had a higher incidence of fibroadenoma than did their control counterparts. It is interesting to note that in male rats, exposure was associated with a decrease in glandular hyperplasia and an increase in fibroadenomas. If tumors are bound to be more common and hyperplasia less so, these questions follow: is exposure converting hyperplastic lesions into neoplasms, or are the two lesions unrelated? Further study and examination are needed to answer these questions.

	601 M : F	602 M : F	603 M : F	604 M : F	605 M : F
% Incidence chronic animals:					
Glandular hyperplasia	24 : 38	13 : 36	2 : 11	2 : 41	10 : 44
Fibroadenoma	1 : 6	8 : 17	13 : 17	10 : 12	10 : 13

NEOPLASIA LIST

AAMRL PROJECT: 601-605

NOTE: Numbers in () represent metastatic tumors.

HISTOLOGIC DIAGNOSIS	601 CONTROLS (M)	(F)	602 JP-7 LOW DOSE (M)	(F)	603 JP-7 HIGH DOSE (M)	(F)	604 JP-TS LOW DOSE (M)	(F)	605 JP-TS HIGH DOSE (M)	(F)
1. NASAL SECTION										
a. Adenoma:	1									
b. Adenocarcinoma:	1									
c. Polyp:	--	--	1	--	1					
2. BONE										
Osteosarcoma:	--	--	1							
3. TRACHEA										
a. Submucosal gland CA:	--	--	--	--	--	--	--	--	1	
b. Undiff. sarcoma:	(1)									
4. ESOPHAGUS										
a. Undiff. sarcoma:	(1)									

AAMRL: neoplasia list, cont.

5. THYROID GLAND											
a. C-cell adenoma:	8	--	10	5	13	6	5	11	5	3
b. C-cell carcinoma:	2	1	4	--	--	1	1	--	1	2
b. Follicular cell carcinoma:	--	--	1	--	--	1	--	1	1	
c. Papillary cyst adenoma:	--	--	--	--	--	--	--	1		
6. PARATHYROID GLAND										
a. Adenoma:	--	--	2	--	1					
b. C-cell carcinoma:	--	(1)								
7. LUNGS										
a. A/B adenoma:	2	--	--	--	--	--	--	--	1	
b. A/B carcinoma:	--	--	1							
c. Osteosarcoma:	--	--	(1)							
d. Squamous cell CA:	--	--	--	--	(1)					
e. Hemangiosarcoma:	--	--	--	--	--	--	--	--	(1)	
f. Islet cell CA:	--	--	--	(1)						
8. HEART										
a. Neurolemoma/ neurinoma:	--	--	--	--	1	--	1	--	1	
b. Neurosarcoma:	--	--	--	--	--	--	--	--	1	
c. Neurofibroma:	--	--	--	1						
d. Atrial/caval epithelial mesothelioma:	1									
e. Undiff. sarcoma:	(1)									

AAMRL: neoplasia list, cont.

9. LIVER												
a. Neoplastic nodule (adenoma):	--	--	--	--	1	--	--	--	1			
b. Hemangiosarcoma:	--	--	--	--	--	--	--	--	(1)			
c. Carcinoma:	--		--	--	(1)							
d. Islet cell CA:	--	--	--	(1)								
e. Mesothelioma:	--	--	(1)									
10. SPLEEN												
a. Malignant fibrous histiocytoma:	--	--	--	--	(1)							
b. Hemangiosarcoma:	--	--	1	--	1	--	--	--	1			
c. Carcinoma:	--	--	--	--	(1)	--	(1)					
d. Islet cell CA:	--	--	--	(1)								
e. Hemangioma:	--	--	1	--	--	--	1					
f. Mesothelioma:	(1)	--	(1)	--	(1)	--	--	--	(1)			
11. MEDIASTINAL LN												
Carcinoma:	--	--	--	--	(1)							
12. MANDIBULAR LN												
a. Islet cell CA :	--	--	--	(1)								
b. Malignant fibrous histiocytoma:	--	--	--	--	(1)							
c. Spindle cell sarcoma:	(1)											

AAMRL: neoplasia list, cont.

13. MESENTERIC LN												
a. Carcinoma:	--	--	--	--	(1)							
b. Islet cell CA:	--	--	--	(1)								
c. Mesothelioma:	--	--	(1)									
d. Mal. fibrous histiocytoma:	--	--	--	--	--	--	(1)					
14. KIDNEYS												
a. Renal Cell adenoma:	--	--	1	--	3	--	--	--		3	1	
b. Sarcoma (stromal nephroma):	--	--	1									
c. Carcinoma:	--	--	--	--	(2)							
e. Mesothelioma:	(1)	--	(1)	--	(1)							
f. Mali. fibrous histiocytoma:	--	--	--	--	--	--	(1)					
15. ADRENAL GLAND												
a. Pheochromocytoma:	11	6	5	3	17	5	7	2		10	6	
b. Cortical adenoma:	1	1	4	2	7	--	6	3		3	--	
c. Carcinoma:	--	--	--	--	2(1)	--	2					
d. Hemangioma:	--	--	--	--	1							
e. Ganglioneuroma:	1	3	--	--	--	--	--	1		--	1	
f. Mesothelioma:	(1)	--	(1)									
16. SALIVARY GLAND												
a. Adenoma:	1											
b. Spindle cell sarcoma:	1											

AAMRL: neoplasia list, cont.

17. STOMACH												
a. Leiomyoma:	--	--	--	1								
b. Adenocarcinoma:	--	--	--	--	1							
c. Hemangiosarcoma:	--	--	--	--	1							
d. Mal. fibrous histiocytoma:	--	--	--	--	(1)							
e. Mesothelioma:	(1)	--	--	--	--	--		(1)	--		(1)	
18. DUODENUM												
a. Adenocarcinoma:	--	--	--	--	--	1						
b. Carcinoma:	--	--	--	--	(1)							
c. Hemangiosarcoma:	--	--	--	--	--	--		--	--		(1)	
d. Mesothelioma:	(1)	--	--	--	--	--		(1)	--		(1)	
19. PANCREAS:												
a. Islet cell adenoma:	3	--	2									
b. Islet cell CA:	--	--	--	1	1							
c. Acinar cell adenoma:	--	--	1	--	1							
d. Mal. fibrous histiocytoma:	--	--	--	--	(1)							
e. Carcinoma:	--	--	--	--	(1)							
f. Hemangiosarcoma:	--	--	--	--	--	--		--	--		(1)	
g. Mesothelioma:	(1)	--	--	--	(1)	--		(2)				
20. ILEUM												
a. Leiomyoma:	--	--	--	--	--	--		1				
b. Carcinoma:	--	--	--	--	(1)							
c. Mesothelioma:	(1)	--	--	--	--	--		(1)				

AAMRL: neoplasia list, cont.

21. COLON																		
a. Hemangiosarcoma:	--	--		--	--		(1)											
b. Mesothelioma:	(1)	--		--	--		--	--		(1)								
22. ANUS																		
a. Leiomyosarcoma:	--	--		--	--		--	--		--	--		--	(1)				
b. Mesothelioma:	(1)	--		--	--		--	--		(1)								
c. Mal. fibrous histioctyoma:	--	--		--	--		--	--		(1)								
23. TESTES																		
a. ICT:	84			82			80			82			78					
b. Mesothelioma:	(1)			(1)			(2)			4(3)			--					
d. Hemangiosarcoma:	(1)																	
24. SEMINAL VESICLE																		
a. Mesothelioma:	(1)	--		--	--		(2)	--		(2)	--		(1)					
b. Hemangiosarcoma:	--	--		--	--		--	--		--	--		(1)					
25. PROSTATE																		
a. Adenoma/cyst adenoma:	--	--		--	--		--	--		2								
b. Mal. fibrous histiocytoma:	--	--		--	--		--	--		(1)								
26. OVARY																		
Granulosa cell tumor:	--	--		--	1													

AAMRL: neoplasia list, cont.

27. UTERUS											
a. Adenocarcinoma:	--	--	--	--	--	--	--	--	--	1
b. Leiomyosarcoma:	--	--	--	--	--	--	--	--	--	1
c. Leiomyoma:	--	--	--	1	--	2				
d. Fibroma:	--	--	--	1						
e. Endometrial stromal polyp:	--	8	--	12	--	3	--	3	--	2
28. URINARY BLADDER										
a. Papilloma:	--	--	1	--	1					
b. Transitional cell carcinoma:	--	--	--	--	--	--	1			
c. Leiomyosarcoma:	--	--	--	--	--	--	--	--	--	(1)
d. Mesothelioma:	--	--	(1)	--	--	--	--	--	--	(1)
29. SKIN										
a. Keratoacanthoma:	2	--	--	--	2	2	2	1	1	2
b. Sq. papilloma:	1	--	--	--	--	--	--	1		
c. Basal cell tumor:	--	--	--	--	2	--	2	--	1	1
d. Fibroma:	--	--	--	--	--	--	--	--	--	2
e. Mast cell tumor:	--	--	--	1						
f. Mal. fibrous histiocytoma:	--	--	--	--	--	--	--	--	--	1
g. Trichoepithelioma:	--	--	--	--	--	--	--	1		
h. Sebaceous adenoma:	--	--	--	--	--	--	1			
i. Mesothelioma:	(1)									

AAMRL: neoplasia list, cont.

30. SUB Q TISSUE												
a. Mal. fibrous histiocytoma:	<<	<<		1	<<		3	<<		2	<<		1	
b. Fibrosarcoma:	<<	<<		1	<<		1							
c. Fibroma:	10	1		9	3		10	1		5	<<		10	
d. Hemangiosarcoma:	1													
e. Lipoma:	1													
f. Sarcoma:	<<	<<		<<	<<		<<	<<		<<	1			
g. Mesenchymoma:	<<	<<		1										
h. Neurofibroma:	1													
i. Undiff. sarcoma:	1													
31. MAMMARY GLAND												
a. Fibroadenoma/ adenofibroma:	1	6		7	15		9	14		7	10		6	11
b. Papillary cyst adenoma:	<<	<<		<<	<<		<<	<<		<<	2			
c. AdenoCA:	<<	1		1	1		<<	1		<<				
d. Polyp:	<<	<<		<<	<<		1							
32. MUSCLE												
a. Fibroma:	<<	<<		<<	<<		<<	<<		<<	<<		1	
b. Mal. fibrous histiocytoma:	<<	<<		<<	<<		<<	<<		1				
c. Carcinoma:	<<	<<		<<	<<		(1)							
d. Mesothelioma:	<<	<<		<<	<<		<<	<<		(2)				
33. NERVE												
Undiff. sarcoma:	<<	<<		1										

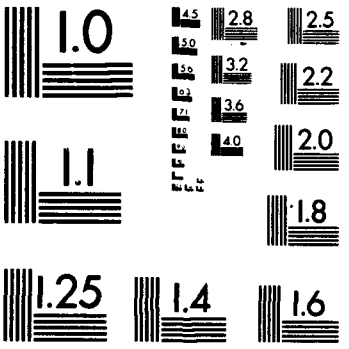
AAMRL: neoplasia list, cont.

34. PITUITARY GLAND											
a. Adenoma:	18	24	21	23	17	24	11	28	14	22	
b. Carcinoma:	--	--	--	--	1	1					
c. Granular cell tumor:	--	--	--	--	--	--	--	1			
35. BRAIN											
a. Astrocytoma:	--	--	--	--	--	--	1	--	--	1	
b. Oligodendroglioma	1	--	--	--	--	--	--	--	--	1	
c. Glioblastoma:	--	--	--	--	1						
d. Granular cell tumor:	--	--	--	--	--	1	1				
e. Glioma:	--	--	--	--	2	--	--	2			
36. ZYMBAL'S GLAND											
a. Adenoma:	1	--	--	--	1	--	--	--	--	1	
b. Carcinoma:	2										
c. Squamous cell CA:	--	--	--	--	1						
37. CLITORAL GLAND											
a. Adenoma:	--	--	--	3							
b. Carcinoma:	--	--	--	--	--	--	--	1			
38. PREPUTIAL GLAND											
a. Adenoma:	--	--	--	--	1	--	--	--	2		
b. Carcinoma:	1	--	2								
c. Squamous cell CA:	1	--	1								

AAMRL: neoplasia list, cont.

39. ABDOMINAL CAVITY																				
a. Mesothelioma:	2	--		3	--		2	--		4	--		2							
b. Mal. fibrous histiocytoma:	--	--		--	--		(1)													
c. Hemangiosarcoma:	--	--		--	--		--	--		--	--		(1)							
40. EYE																				
Undiff. sarcoma:	1																			
41. EAR																				
Neurofibroma:	--	--		--	--		--	--		--	1		2							
42. JEJUNUM																				
a. Leiomyoma:	--	--		--	--		--	--		1										
b. Leiomyosarcoma:	--	--		--	--		--	--		--	--		--	1						
43. VAGINA																				
a. Leiomyosarcoma:	--	--		--	--		--	--		--	1									
b. Fibroma:	--	--		--	--		--	--		--	1									
44. RENAL LN																				
Pheochromocytoma:	--	--		--	--		(1)													
45. SPINAL CORD:																				
Meningioma:	--	--		--	--		--	1												

AD-A252 012 TUMORIGENIC EVALUATION OF JET FUELS JP-TS AND JP-7(U) 2/2
MANTECH ENVIRONMENTAL TECHNOLOGY INC DAYTON OH
R K HARRIS ET AL. APR 91 AL**-TR-1991-0020
UNCLASSIFIED F33615-90-C-0532 NL



SUMMARY OF MAJOR PATHOLOGIC FINDINGS IN F-344 RATS EXPOSED TO JP-7 AND JP-TS VAPORS FOR 365 DAYS CONTINUOUSLY AND THEN HELD FOR LONG-TERM STUDY.

The most significant findings in these animals were the variety and increased incidence of renal disease in male rats, similar to changes reported with JP-5 exposure. The dramatic appearance and disappearance of what are thought to be alpha 2μ globulin was also thought to be significant. Furthermore, renal neoplasms, though increased only slightly in numbers, were thought to be definitely exposure and dose related. Hepatocellular alterations, or foci, unlike those in the earlier JP-5 study did not increase.

Appendix H. Pathologic Findings in Male and Female C57BL/6 Mice Exposed to JP-TS and JP-7 Vapors for One Year and Held for One-Year Postexposure

DISCUSSION OF PATHOLOGIC FINDINGS IN C57BL/6 MICE
EXPOSED TO JP-7 AND JP-TS VAPORS FOR 365 DAYS CONTINUOUSLY AND HELD FOR
LONG-TERM STUDY (EXPTS. #601, 602, 603, 604, AND 605)

1. SKIN AND SUBCUTIS: Chronic, often ulcerative, dermatitis was observed commonly in all groups without an apparent dose response relationship. Chronic dermatitis secondary to trauma is considered to be a common occurrence in the C57BL/6 mouse. Few neoplasms were observed in the skin or the subcutis.

2. MUSCULOSKELETAL SYSTEM: Granulocytic hyperplasia of the bone marrow was fairly common in all groups and was occasionally associated with inflammation, such as chronic ulcerative dermatitis. Granulocytic hyperplasia was reported as a fairly common change in the JP-5 study and by Firth, et.al.

3. RESPIRATORY SYSTEM:

a. NOSE. Hyaline degeneration of the mucosal and submucosal gland epithelium was prevalent in all groups. There was a fairly marked variability between groups and a slightly increased frequency in treatment groups versus control groups, although no dose response relationship was evident. Variables making this a difficult change to assess include: the location of the section through the nose, with severity and incidence increased in the more posterior (toward the nose) sections; the quality of the stain, with more intensely stained sections better demonstrating the lesion; and, the meticulousness taken by the pathologist to examine each section, as the change often involves only a short segment of the mucosa. The increased prevalence of hyaline degeneration in control mice compared to treatment groups reported in the JP-5 study was not apparent for either of the two fuels tested in this study.

b. LUNG:

(1) Lymphoid infiltrates were common in all chronic groups, particularly in the females, and generally in a higher frequency than reported by Firth, et.al. Eosinophilic crystals were less common than reported in the JP-5 study, but were slightly more common than reported by Firth, et.al.

(2) Primary lung tumors in male mice occurred in a slightly higher frequency than reported by Firth, et.al. and were the most numerous in control groups. As observed in the JP-5 study, JP-7 and JP-TS do not appear to be significant pulmonary carcinogens for C57BL/6 mice.

c. NASOLACRIMAL DUCT: Hyperplasia and inflammation were common in all groups and slightly higher in frequency in treatment groups, although no dose response relationship was evident. These changes seemed to vary according to

ATCH 1

where the section was taken, with lesions diagnosed more frequently when sections were taken posteriorly.

4. CARDIOVASCULAR SYSTEM: Not remarkable.

5. LYMPHORETICULAR SYSTEM:

a. MALIGNANT LYMPHOMA: Malignant lymphoma, common in the C57BL/6 mouse, was frequently observed in all chronic experimental groups with no dose response relationship. The incidence in this study (60% in female controls) was appreciably greater than reported in the JP-5 study (11.4%) and in the Firth paper (36.8%). Lymphoid hyperplasia and malignant lymphoma in the lymphoreticular organs, and lymphocytic inflammation in non-lymphoid organs such as the salivary gland, liver, lung, and kidney increased with age; the morphologic difference between inflammation, hyperplasia and neoplasia was often blurred. The incidence of malignant lymphoma in each of the experimental groups is as follows:

	Exp 601 Male	Exp 602 Male	Exp 603 Male	Exp 604 Male	Exp 605 Male
Acute	0	0	1(4%)	1(3%)	1(3%)
Chronic	17(25%)	17(23%)	16(22%)	16(25%)	16(23%)
	Exp 601 Female	**Exp 602 Female**	**Exp 603 Female**	**Exp 604 Female**	**Exp 605 Female**
Acute	1(4%)	1(3%)	0	0	0
Chronic	43(60%)	17(29%)	31(45%)	27(35%)	39(49%)

b. SPLEEN: Extramedullary hematopoiesis (EMH) is physiologic in the spleen of mice. In this study, it was diagnosed when considered excessive; it was diagnosed frequently in all experimental groups with no dose response relationship.

6. DIGESTIVE SYSTEM:

a. NEOPLASIA: Neoplasms (other than malignant lymphoma) were only observed in treatment groups, but with the exception of intestinal adenoma, no more than one neoplasm was diagnosed in a particular segment of the gastrointestinal tract in each experimental group. The number of adenomas observed in all male treatment groups was higher than reported in the cited

studies, however no dose response relationship is apparent. The incidence of gastrointestinal neoplasia in each of the experimental groups is as follows:

DIGESTIVE SYSTEM - NEOPLASM INCIDENCE IN CHRONIC GROUPS

Lesion	Exp 601 Male:Female	Exp 602 Male:Female	Exp 603 Male:Female	Exp 604 Male:Female	Exp 605 Male:Female
Oral Squamous Cell Carcinoma:	-0-	-0-	-0-	-0-	0:1[3]
Gastric Polyp:	-0-	-0-	-0-	-0-	-0-
	-0-	-0-	-0-	-0-	(1.5%)1:0
Small Intestine:[1]					
Hyperplasia:	-0-	-0-	-0-	-0-	-0-
	-0-	0:1(2%)	-0-	-0-	0:2(3%)
Adenoma:	-0-	-0-	-0-	-0-	-0-
	-0-	(4%)3:1(2%)	(4%)3:2(3%)	(5%)3:0	2:0
Carcinoma	-0-	-0-	-0-	-0-	-0-
	-0-	-0-	-0-	-0-	0:1[3]
Large Intestine:[2]					
Hyperplasia:	-0-	-0-	-0-	-0-	-0-
	-0-	-0-	0:1(2%)	-0-	0:1(3%)
Adenoma:	-0-	-0-	-0-	-0-	-0-
	-0-	0:1(3%)	-0-	0:1(2%)	-0-
Leiomyoma:	-0-	-0-	-0-	-0-	-0-
	-0-	-0-	-0-	0:1[3]	-0-
Leiomyosarcoma:	-0-	-0-	-0-	-0-	-0-
	-0-	-0-	-0-	0:1(2%)	-0-
Mesentery:					
Fibrosarcoma:	-0-	-0-	-0-	-0-	-0-
	-0-	-0-	-0-	0:1[3]	-0-
Hemangioma:	-0-	-0-	-0-	-0-	-0
	-0-	-0-	-0-	-0-	1:0[3]

[1]Duodenum and jejunum combined.
[2]Colon, cecum, rectum, and anus combined.
[3]Non-protocol tissue; % not applicable.

b. AMYLOIDOSIS: Amyloid was diagnosed in the small intestine with somewhat increased frequency in chronic treatment groups versus controls.

c. STOMACH: Gastric ulcers and hyperkeratosis were observed in a slightly increased frequency in the female chronic high dose JP-TS (605) group compared to controls.

7. LIVER AND PANCREAS: Hepatic neoplasms (adenomas and carcinomas) were observed in about the same frequency in all experimental groups and occurred in a frequency comparable with the cited references. Hepatocellular fatty change was common in all treatment groups and was often associated with disease processes occurring elsewhere in the body. Inflammation was more frequently observed in the livers of low and high dose chronic female groups versus controls. The high incidence of lymphoid infiltrates and extramedullary hematopoiesis observed in in the livers of all female groups, and the difficulty distinguishing these two morphologic categories from inflammation, probably makes this an insignificant finding. The hepatic inflammation generally was mild.

8. URINARY SYSTEM: Histologic interpretation of renal glomerular changes was found to be a real challenge due to the increased thickening of glomerular tufts associated with aging in the C57BL/6 mouse. Glomerulonephritis was diagnosed when there was marked thickening of a majority of tufts with homogeneous, eosinophilic deposits. The material deposited in the more severely affected glomeruli often resembled amyloid; congo red staining of the amyloid-like deposits in general was equivocal. All groups, males and females, except for the JP-TS (605) group, exhibited glomerular changes in a frequency similar to that reported in the cited literature. The incidence and severity grade of glomerulonephritis was slightly higher in the males and females in the chronic JP-TS (605) group compared to the control group; there was no dose response relationship. It is probably prudent to compare this finding with previous and future hydrocarbon studies.

9. ENDOCRINE SYSTEM:

a. ADRENAL GLAND: Cortical hyperplasia was diagnosed commonly in all chronic male groups without a dose response relationship. Capsular cell hyperplasia was present in a high frequency in all groups of female mice, acute and chronics; it was less common and less severe in males.

b. PITUITARY: Pituitary adenomas and hyperplasias were observed in high frequency in all chronic female groups. Interestingly, the frequency was markedly higher than reported in the sited references. There was no dose response relationship.

c. THYROID: Cystic follicles were common in all female groups. There was a slightly higher incidence of cystic follicles in the high dose chronic JP-TS (605) female group compared to controls. This is probably is not a significant finding as follicular cysts are considered a common aging change in the C57BL/6 mouse. Follicular hyperplasias and adenomas were diagnosed more often in females with no dose response relationship.

10. REPRODUCTIVE SYSTEM:

a. UTERUS: Endometrial cysts and sclerosis were observed commonly in all chronic groups without a dose response relationship.

b. OVARY: Angiectasis was diagnosed slightly more often in the ovaries of the high dose groups compared to controls, and was observed more frequently than described by Firth, et.al. Atrophy was diagnosed commonly in all chronic groups without a dose response relationship.

11. CENTRAL NERVOUS SYSTEM: Not remarkable.

12. SPECIAL SENSES:

EYE: Of particular interest was the high incidence of cataracts in female mice and keratitis (listed as inflammation in the printouts) in all chronic groups. Neither change was mentioned in the JP-5 report, while cataracts were occasionally observed by Firth, et.al. No dose response relationship was evident. Eyes from male mice in the control and high dose groups were reevaluated; occasional cataracts and keratitis were observed in males, but not nearly in the frequency seen in the females.

SUMMARY OF MAJOR PATHOLOGIC FINDINGS IN C57-BL/6 MICE EXPOSED TO JP-7 AND JP-TS VAPORS FOR 365 DAYS CONTINUOUSLY AND HELD FOR LONG-TERM STUDY

There was no distinct evidence that exposure to JP-7 or JP-TS vapors resulted in accelerated degenerative changes or increased carcinogenesis in any major organ system. The slight increase in numbers of neoplasms in the gastrointestinal tract compared to controls in this study, and to cited literature, indicates that gastrointestinal neoplasia should be carefully evaluated in future hydrocarbon studies.

SECTION 5

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QUALITY ASSURANCE

The study, "Oncogenic Evaluation of Jet Fuels JP-TS and JP-7," was conducted by the University of California, Irvine., Toxic Hazards Research Unit under the guidance of the Environmental Protection Agency's Good Laboratory Practices Guidelines, 40CFR PART 792. This report was prepared by ManTech Environmental Technology, Inc. No claim will be made that this was a "GLP" study as no attempt was made to adhere to the strict requirements of these guidelines. The various phases of this study were inspected by members of the Quality Assurance Unit. Results of these inspections were reported directly to the Study Director at the close of each inspection.

DATE OF INSPECTION:	**ITEM INSPECTED:**
June 12, 1981	Chemistry data sheets.
July 9, 1981	Chemistry data records.
August 14, 1981	QC data.
April 2, 1982	Study records.
July 20, 1982	Chemistry final report.
October 6, 1982	Chemistry final report.
November 3, 1982	Chemistry final report.
February 25 - March 1, 1991	Study data and final report audit.

The Quality Assurance Unit has determined by review process that this report accurately describes those methods and standard operating procedures required by the protocol and that the reported results accurately reflect the raw data obtained during the course of the study. No discrepancies were found that would alter the interpretation presented in this Final Report.

M. G. Schneider
QA Coordinator
Toxic Hazards Research Unit

Date April 1, 1991